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Therapeutic Review
β_2-Agonist Single Agents

Overview/Summary

Respiratory β_2-agonists are primarily used to treat reversible airway disease. Their Food and Drug Administration (FDA)-approved indications include asthma, chronic obstructive pulmonary disease (COPD), exercise-induced asthma/bronchospasm (EIA), and/or and reversible bronchospasm. Respiratory β_2-agonists relax the smooth muscles from the trachea to the terminal bronchial tree, resulting in bronchodilation and allowing patients to breathe more easily.[1-4]

The β_2-agonists can be divided into two categories: short acting and long acting. The short-acting respiratory β_2-agonists (SABAs) consist of albuterol, levalbuterol, metaproterenol, pirbuterol, and terbutaline. The long-acting β_2-agonists (LABAs) include extended release albuterol, arformoterol, formoterol, and salmeterol. Respiratory β_2-agonists elicit a similar biologic response in patients suffering from reversible airway disease, but differ in their dosing requirements, pharmacokinetic parameters, and potential adverse effects.[5-19]

As a result of the Clean Air Act and the Montreal Protocol on Substances that Deplete the Ozone Layer, the FDA made the decision to end production, marketing, and sale of all albuterol MDIs containing chlorofluorocarbons (CFCs) as their propellant by December 31, 2008. Currently all CFC MDIs are being replaced by MDIs that utilize hydrofluoroalkanes (HFAs) as their propellants. HFA inhalers provide the same level of safety and efficacy as CFC inhalers, but without harming the ozone layer. There may be a few differences in taste and/or feel with HFAs compared to CFCs.[5-7,20]

According to the National Heart, Lung, and Blood Institute (NHLBI)/National Asthma Education and Prevention Program (NAEPP) and the Global Initiative for Asthma (GINA), inhaled corticosteroids (ICSs) are the most effective long-term control medications used for the treatment of asthma for patients of all ages.[1,2] Alternative long-term control medications include leukotriene modifiers, mast-cell stabilizers, and methylxanthines, however these agents are considered less effective as monotherapy compared to ICSs. LABAs should not be used as monotherapy for the management of asthma; however, they are considered the most effective adjunctive therapy in patients who are not adequately controlled with an ICS alone. Leukotriene modifiers, mast-cell stabilizers, and methylxanthines may also be used as adjunctive therapies but are less effective than the LABAs. Chronic administration of systemic corticosteroids is reserved for severe, difficult-to-control asthma patients and the use of immunomodulators is only indicated in asthma patients with severe disease and allergies.

Current clinical guidelines also state that SABAs are the medication of choice for the relief of bronchospasm during acute exacerbations of asthma.[1,2] Anticholinergics may also be used for the treatment of acute exacerbations but are considered less effective than SABAs.[1] The addition of a systemic corticosteroid may be required if patients do not respond immediately to treatment with a SABA or if the exacerbation is severe.[2] According to the NHLBI/NAEPP, the use of LABAs to treat acute symptoms or exacerbations of asthma is not currently recommended.[1]

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, agents used to manage stable chronic obstructive pulmonary disease include inhaled bronchodilators and corticosteroids.[3] The choice between bronchodilators, which are central to COPD symptom management, depend on patient response, the incidence of adverse events, and availability. Bronchodilators, which include long- and short-acting β_2-agonists, anticholinergics, and methylxanthines, should be administered as needed or on a scheduled basis to relieve intermittent or worsening symptoms or to prevent or reduce

persistent symptoms. Long-acting bronchodilators are more effective and convenient than short-acting bronchodilators however short-acting bronchodilators should be considered initial empiric therapy.[3,4] According to the National Institute for Clinical Excellence, long-acting bronchodilators should be used to control symptoms of COPD in patients who continue to experience problems despite the use of short-acting bronchodilators.[4] Also, a combination of bronchodilators from different pharmacologic classes may increase the efficacy of the treatment regimen. The addition of an inhaled corticosteroid to a treatment regimen reduces exacerbations and improves lung function.[3] Long-term treatment with oral corticosteroids is not recommended for the management of stable COPD.

Current GOLD guidelines also recommend the use of bronchodilators and corticosteroids for the management of acute COPD exacerbations.[3] An increase in the dose and/or frequency of short-acting bronchodilators as well as the addition of an anticholinergic until symptoms improve is recommended. For patients with a baseline Forced Expiratory Volume in one second (FEV_1) <50% predicted, the addition of oral corticosteroids is recommended for the management of acute exacerbations. The use of antibiotics in COPD is only recommended for the treatment of infectious exacerbations.

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Short Acting β_2-agonists		
Albuterol (AccuNeb®, ProAir HFA®, Proventil HFA®, Ventolin HFA®, Vospire ER®)	β_2-agonists	✔
Levalbuterol (Xopenex HFA®)	β_2-agonists	-
Metaproterenol (Alupent®)	β_2-agonists	✔
Pirbuterol (Maxair Autohaler®)	β_2-agonists	-
Terbutaline (Brethine®)*	β_2-agonists	✔
Long Acting β_2-agonists		
Arformoterol (Brovana®)	β_2-agonists	-
Formoterol (Foradil®)	β_2-agonists	-
Salmeterol (Serevent Diskus®)	β_2-agonists	-

HFA=hydrofluoroalkanes.

Indications

Table 2. Food and Drug Administration Approved Indications[5-19]

Generic Name	Asthma	Chronic Obstructive Pulmonary Disease	Exercise Induced Asthma	Reversible Bronchospasm
Short Acting β_2-agonists				
Albuterol	✔		✔	✔
Levalbuterol	✔			✔
Metaproterenol	✔			✔
Pirbuterol*	✔			✔
Terbutaline	✔			✔
Long Acting β_2-agonists				
Arformoterol	-	✔†		
Formoterol‡	✔	✔†	✔	✔
Salmeterol§	✔	✔†	✔	✔

* Approved for concomitant use with theophylline and/or corticosteroid therapy.
† Patients who require regular treatment with inhaled short-acting β_2-agonists; not indicated for patients whose asthma can be managed by occasional use of inhaled short-acting β_2-agonists.
‡ Approved for concomitant use with short-acting β_2-agonists, inhaled or systemic corticosteroids, and theophylline.
§ Approved for concomitant use with inhaled or systemic corticosteroid therapy.

Pharmacokinetics

Table 3. Pharmacokinetics[5-19]

Generic Name	Onset of Action (minutes)	Duration of Action (hours)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Short Acting β_2-agonists					
Albuterol (HFA-propelled inhalation)	8.2-10.0* 6-7† 5.4-7.8‡	2.3-6.0	80-100	Yes	3.0-7.5
Albuterol (nebulized inhalation)	30-60	2.5-6.0	80-100	Yes	4.6-6.0
Albuterol (oral tablets)	2-6	4-6	76	Yes	5.0-9.3
Levalbuterol	5-17	3-6	80-100	Yes	3.3-4.0
Metaproterenol	1-30	1-5	Not reported	Not reported	Not reported
Pirbuterol	5-30	3-4	51	Yes	2-3
Terbutaline	5-45	1.5-8.0	30-90	No	2.9-14.0
Long Acting β_2-agonists					
Arformoterol	7-20	12	67	No	26
Formoterol	1-3	8-12	15-18	No	7-14
Salmeterol	10-20	12	25	No	5.5

HFA=hydrofluoroalkanes.
*ProAir HFA®.
†Proventil HFA®.
‡Ventolin HFA®.

Clinical Trials

Clinical trials have demonstrated the efficacy of short-acting and long-acting β_2-agonists (SABAs and LABAs) in providing relief of asthma exacerbations, chronic obstructive pulmonary disease (COPD) exacerbations, and exercise induced asthma (EIA). National and international treatment guidelines recognize the efficacy of these agents for their respective indications and note that all available agents are equally efficacious; giving no preferential status to one agent over another.[1-4]

In the clinical trials for the treatment of mild asthma, all SABAs have been shown to be efficacious in improving Forced Expiratory Volume in 1 second (FEV_1). There have been several studies conducted comparing albuterol to levalbuterol; these studies have shown inconsistent results resulting in the inability to definitively give preference to one agent over the other.[21-31] In two studies (one retrospective, one prospective), levalbuterol resulted in a significantly lower hospitalization rate compared to albuterol.[21,22] In another trial, when the two agents were given in the emergency department, there was no significant difference in the time to discharge.[24] In one unpublished study, the difference in peak FEV_1 was statistically significant for albuterol HFA compared to levalbuterol HFA (P=0.018).[30] Additionally, studies have shown no significant differences between the two agents in the peak change in FEV_1 and the number and incidence of adverse events experianced.[21-31]

The LABAs salmeterol and formoterol have been found to improve FEV_1 in patients with mild to moderate asthma who require persistent use of SABAs. The SMART trial found that salmeterol had a significant occurrences of combined respiratory related deaths or respiratory related life-threatening experiences compared to placebo (P<0.05).[41] In a meta-analysis by Salpeter et al, salmeterol and formoterol both demonstrated an increase in severe exacerbations that required hospitalization, life threatening exacerbations, and asthma-related deaths in adults and children alike when compared to placebo.[33] Due to the results of these studies, salmeterol, formoterol, and arformoterol have a black box warning stating that these agents may increase the risk of asthma related deaths.[11,14,16]

For the treatment of COPD, national and international guidelines state that no medication has been shown to modify the long-term decline in lung function associated with COPD. Guidelines recommend that treatment should be focused on reducing the symptoms and complications of the disease.[3,4] All the agents used in the treatment of COPD (i.e., inhaled corticosteroids, inhaled anticholinergics, β_2-agonists, and methylxanthines) can improve symptoms, exacerbations, and complications of the disease. Long-acting bronchodilators are more effective and convenient than short-acting bronchodilators; however, short-acting bronchodilators should be considered initial empiric therapy.[1,2] In two studies patients diagnosed with COPD were treated with arformoterol, salmeterol, or placebo and found that both arformoterol and salmeterol significantly improved morning trough FEV_1 throughout the 12 weeks of daily treatment compared to placebo (P<0.001 in both trials).[54,55] Currently, there are a lack of head-to-head randomized, double blind, clinical trials to determine a preferential status of one agent over another for the treatment of COPD.

For the treatment of EIA, albuterol, metaproterenol, and formoterol have demonstrated an improvement in FEV_1 compared to placebo.[52-66] In one study, albuterol and metaproterenol treated patients had a lower incidence of exercised induced bronchospasm compared to placebo.[62] In another study comparing albuterol, formoterol and placebo for EIA, both active treatment groups provided a statistically significant decrease in mean maximum percent of FEV_1 compared to placebo (P<0.01).[63]

Overall, head-to-head clinical trial results were inconsistent to determine preferential status of one agent over another. Clinical studies evaluating the safety and efficacy of the SABAs and LABAs are summarized in Table 4.

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Asthma				
Carl et al[21] Albuterol 2.5 mg via nebulization (every 20 minutes for 2 hours) vs levalbuterol 1.25 mg via nebulization (every 20 minutes for 2 hours)	DB, PRO, RCT Individuals 1 to 18 years old with diagnosed with asthma presenting to the emergency department (1 patient had been using levalbuterol the remainder albuterol as rescue prior to presenting to the emergency department)	N=547 Varying duration of hospitalizations	Primary: Hospital admission rate Secondary: LOS, ED LOS, intensification, number of aerosols, requirement for oxygen, and adverse effects	Primary: Compared with the albuterol group (45%), the levalbuterol group (36%) had a significantly lower hospitalization rate (*P*=0.02). Secondary: There were no significant differences between the albuterol and levalbuterol group concerning secondary outcomes, including adverse effects (*P*=0.26 to *P*=0.94). No significant adverse events occurred in either group.
Schreck et al[22] Albuterol 2.5 mg via nebulization (plus standard treatment) vs levalbuterol 1.25 mg via nebulization (plus standard treatment)	CR, OS, RETRO, Individuals 1 year of age or older with a diagnosis of acute asthma presenting to the ED requiring nebulization with a SABA	N=736 9 months	Primary: Patient disposition, ED LOS, and objective measures of patient upon arrival Secondary: Not reported	Primary: There was a significantly lower hospitalization rate in the levalbuterol group compared with albuterol (4.7% and 15.1%; *P*=0.0016). The rate of 15.1% is comparable to the hospitals average admission rate of 16.4%. There was no significant difference between the two treatment groups concerning ED LOS and other objective measures upon patient presentation (*P*=0.762). Due to a decrease in hospitalizations, treatment costs were lower in the levalbuterol treatment group (no *P* value reported). Secondary: Not reported
Qureshi et al[23] Albuterol 2.5-5 mg via nebulization (plus standard	DB, PRO, RCT Children 2 to 14 years old with a known history of	N=129 Study was complete after patient received	Primary: Changes from baseline in clinical asthma score and the percent of	Primary: No significant differences between the treatment groups were found (no *P* value reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
treatment as needed) vs levalbuterol 1.25-2.5 mg via nebulization (plus standard treatment needed)	asthma presenting to a pediatric ED with an acute moderate or severe asthma exacerbation	5 doses, was admitted, or discharged	predicted FEV_1 after the 1st, 3rd, and 5th treatment Secondary: Number of treatments, length of ED care, rate of hospitalizations, changes in pulse rate, and oxygen saturation	Secondary: No significant differences between the treatment groups were found (no *P* value reported). No significant differences between the treatment groups concerning adverse effects (no *P* value reported).
Skoner et al[24] Albuterol 1.25 mg via nebulization vs albuterol 2.5 mg via nebulization vs levalbuterol 0.31 mg via nebulization vs levalbuterol 0.63 mg via nebulization vs placebo	DB, MC, PC, PG, RCT Children 2 to 5 years old who have been diagnosed with asthma for at least 30 days and had no other underlying medical condition	N=211 4 weeks	Primary: Change from baseline in the total score on the PAQ Secondary: PEF, rescue medication use, and the Child Health Status Questionnaire	Primary: Decrease in the PAQ scores was demonstrated in all treatment groups (no *P* value reported). Secondary: All treatment groups demonstrated an improvement in PEF compared to placebo (*P*<0.01 for all treatment groups). All treatment groups, including the placebo group, demonstrated a decrease in rescue medication use. There were no significant differences between the treatment groups (No *P* value reported). All treatment groups demonstrated and improvement from baseline in the Child Health Status Questionnaire (no *P* value reported). Overall, the incidence of adverse events was similar for each treatment group during the study period. Adverse events were mild (68.0%) to moderate (28.1%) in severity. Among all patients, significant increases in ventricular heart rate were demonstrated in the levalbuterol 0.63 mg and racemic albuterol 2.5 mg groups compared to placebo (no *P* value reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Nowak et al[25] Albuterol 2.5 mg via nebulization (up to 6 doses in 3 hours) with prednisone 40 mg tablet vs levalbuterol 1.25 mg via nebulization (up to 6 doses in 3 hours) with prednisone 40 mg tablet	DB, MC, PG, PRO, RCT Individuals ≥18 years old presenting to the ED or clinic with an acute asthma exacerbation	N=627 1 month	Primary: Time to meet ED discharge criteria Secondary: Comparisons of FEV_1 change from baseline, the proportion of patients hospitalized, and the effect of plasma concentration of (*S*)-albuterol at presentation on FEV_1 response and on hospitalization	Primary: For the levalbuterol and albuterol groups the median time to discharge (76.0 and 78.5 minutes) was not statistically different (*P*=0.74). Secondary: There was no significant difference (*P*=0.28) in the admission rate between the albuterol (9.3%) and the levalbuterol (7.0%) groups. After dose one and cumulative doses over time there was a greater FEV_1 improvement following levalbuterol compared with albuterol (*P*=0.021). For individuals not taking corticosteroids chronically before the trial, there were significantly fewer hospitalizations in the levalbuterol group compared to albuterol (3.8% vs 9.3%; *P*=0.03). There was no significant difference in the overall frequency of adverse effects in the two treatment groups (no *P* value reported).
Nelson et al[26] Albuterol 1.25 mg TID via nebulization vs albuterol 2.5 mg TID via nebulization vs levalbuterol 0.63 mg TID via nebulization vs levalbuterol 1.25 mg	DB, PC, PG, RCT Patients ≥12 years old that do not smoke and had at least a 6-month history of chronic and stable asthma, demonstrating at least a 15% improvement in FEV_1 to a single dose of albuterol 2.5 mg via nebulization	N=362 4 weeks	Primary: Peak change in FEV_1 after 4 weeks Secondary: AUC, use of rescue racemic albuterol meter dose inhaler	Primary: Change in peak FEV_1 in the combined levalbuterol group was not significantly greater than combined albuterol (0.84 and 0.74; no *P* value reported). Secondary: A similar trend was noticed when evaluating the AUC; after the first dose, levalbuterol treatment was significantly better (*P*=0.02) compared to albuterol. However, at week 4, even though the AUC values were higher in the levalbuterol groups, the difference was not significant. There was a significant improvement (*P*=0.006) in predose FEV_1 in the combined levalbuterol arm compared to the combined albuterol arm in the subset of patients not taking corticosteroids. There was significantly less rescue medication used in the active treatment groups compared to placebo. Compared to baseline there was a significant decrease in rescue-medication use in both the levalbuterol

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
TID via nebulization vs placebo				1.25 mg arm (*P*<0.001) and the albuterol 2.5 mg arm (*P*=0.056). All active treatments were well tolerated with the percent of patients reporting nervousness or tremor in the low dose groups being statistically significantly lower (*P*=0.003) compared to the high dose groups.
Gawchik et al[27] Albuterol 1.25 mg via nebulization (1 dose) vs albuterol 2.5 mg via nebulization (1 dose) vs levalbuterol 0.16 mg via nebulization (1 dose) vs levalbuterol 0.31 mg via nebulization (1 dose) vs levalbuterol 0.63 mg via nebulization (1 dose) vs	DB, PC, RCT, XO Patients 3 to 11 years old with a history of asthma for at least 6 months and reversibility of 12% or more 30 minutes after 2.5 mg of albuterol administered by nebulization	N=43 4 treatment visits (2 to 8 days apart)	Primary: Differences in peak change in FEV_1, peak percent change in FEV_1 and AUC Secondary: Not reported	Primary: Differences in peak change in FEV_1, peak percent change in FEV_1 and AUC was significantly improved in all treatment arms (with the exception of albuterol 1.25 mg in AUC) compared with placebo (*P*<0.05). No significant differences between the treatment groups were found (*P*<0.55). The medications were well tolerated and all adverse events reported were mild or moderate in severity, with no significant difference seen across the treatment groups (no *P* values reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
levalbuterol 1.25 mg via nebulization (1 dose) vs placebo (1 dose)				
Milgrom et al[28] Albuterol 1.25 mg via nebulization vs albuterol 2.5 mg via nebulization vs levalbuterol 0.31 mg via nebulization vs levalbuterol 0.63 mg via nebulization vs placebo	DB, MC, PC, PG, RCT Patients 4 to 11 years old with documented diagnosis of at least mild asthma with a reversibility of at least 15% to albuterol	N=338 3 weeks	Primary: Peak percent change in FEV_1 from baseline Secondary: Change in pulmonary function, percent of responders within 30 minutes after dose, time to peak improvement in FEV_1, use of rescue medications, symptoms, symptom-free days, asthma control days, and adverse effects	Primary: A significant improvement was seen in peak percent change in FEV_1 from baseline in all active treatment arms compared with placebo on day 21 (P<0.019). Secondary: Immediately after nebulization on days 0 and 21 there were clinically significant changes for all groups except placebo (P<0.02) and, with the exception of the albuterol 1.25 mg group, more patients responded to active treatment in comparison to the placebo group on both days (P<0.02). On day 0 significantly more patients responded to levalbuterol 0.31 mg (62.9%) than to albuterol 1.25 mg (41.8%), immediately after nebulization (P=0.12). Levalbuterol 0.31 mg achieved a significantly greater change in asthma control days compared to levalbuterol 0.63 mg and albuterol 1.25 mg (P<0.04 for each comparison). Compared to all active treatments levalbuterol 0.31 mg produced significantly smaller changes in heart rate (P<0.02). A significant decrease in potassium levels was seen in all treatment groups compared to placebo (P<0.002).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Data of file[29] Albuterol 180 µg QID via HFA-MDI vs levalbuterol 90 µg QID via HFA-MDI vs placebo	DB, PC, PG, RCT Patients ≥12 years old with moderate to severe asthma with a FEV_1 45%-75% of the predicted value	N=445 9 weeks	Primary: Mean percent change in peak FEV_1 Secondary: Not reported	Primary: Levalbuterol HFA and albuterol HFA demonstrated a significant improvement in mean peak FEV_1 during the study period compared to placebo (25.63%, 28.98% vs 13.94%, respectively; *P*<0.001). The difference in peak FEV_1 was statistically significant for albuterol HFA compared to levalbuterol HFA (*P*=0.018). Overall, the incidences in adverse events were similar between all treatment groups. The most commonly reported adverse events were headache, viral infection, and asthma. However, the most common adverse event leading to discontinuation was asthma that occurred in 5.5%, 2.5%, and 1.8% of patients in the levalbuterol HFA, albuterol HFA, and placebo groups, respectively. Secondary: Not reported
Data of file[30] Albuterol 180 µg QID via HFA-MDI vs levalbuterol 90 µg QID via HFA-MDI vs placebo	DB, PC, PG, RCT Patients ≥12 years old with moderate to severe asthma with a FEV_1 45%-75% of the predicted value	N=303 9 weeks	Primary: Mean percent change in peak FEV_1 Secondary: Percentage of responders, defined as patients achieving a FEV_1 value >15% over the visit predose value	Primary: Levalbuterol HFA and albuterol HFA demonstrated a significant improvement in mean peak FEV_1 during the study period compared to placebo (25.30%, 26.14% vs 12.45%, respectively; *P*<0.001). Secondary: The percentage of responders was greater in each active treatment group compared to placebo at each visit. The time to 15% response was also significantly shorter for each active treatment group compared to placebo at visits 2 and 6 (*P*<0.001). Overall, the incidences in adverse events were similar between each treatment groups (50.0% to 56.5%). Serious adverse events were slightly less common in the levalbuterol HFA group (5.7%) compared to the albuterol HFA (10.0%) and placebo (8.5%) groups. Adverse event leading to discontinuation occurred in 5.7%, 10.0%, and 6.8% of patients in the levalbuterol HFA, albuterol HFA, and placebo groups, respectively.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Nowak et al[28] Albuterol 2.5 mg via nebulization (3 doses) vs albuterol 5 mg via nebulization (3 doses) vs levalbuterol 0.63 mg via nebulization (3 doses) vs levalbuterol 1.25 mg via nebulization (3 doses) vs levalbuterol 2.5 mg via nebulization (3 doses) vs levalbuterol 3.75 mg via nebulization (3 doses) vs levalbuterol 5 mg via	OL, PRO Adult asthmatics presenting to the ED with an acute asthma exacerbation	N=93 2 hours	Primary: FEV_1 percent change from baseline following the 3rd nebulization Secondary: Change and percent change from baseline FEV_1 at each time point, the percent of responders, and the time to achieve a 15% and 50% increase from baseline	Primary: The median percent change in FEV_1 was greater for 1.25 mg levalbuterol (74%), compared with 2.5 mg albuterol, (39%), 0.63 mg levalbuterol (37%), and 3.75 mg levalbuterol (26%) after three doses (no *P* value reported). Secondary: Compared to baseline at 60 minutes post treatment, levalbuterol 1.25, 2.5, and 5.0 mg improved the median percent predicted FEV_1 by 33%-38% compared to 12%-24% with 2.5 and 5.0 mg doses of albuterol and 0.63 and 3.75 mg doses of levalbuterol (no *P* value reported). (*S*) albuterol levels were found to be significantly inversely correlated with baseline FEV_1 (*P*=0.004), and percent change in FEV_1 60 minutes post dose (*P*=0.006).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
nebulization (3 doses)				
Wolfe et al[32] Albuterol syrup 2 mg TID vs metaproterenol syrup 10 mg TID	IB, MC, PG, RCT Individuals 5 to 9 years old with chronic asthma	N=65 4 weeks	Primary: Time to maximal response, maximum percent increase from baseline, peak flow measurements, heart rate, blood pressure, adverse effects Secondary: Not reported	Primary: There was a significantly greater degree of bronchodilation with albuterol compared to metaproterenol from 2-8 hours post dose (P<0.05). The peak percent improvement in FEV_1 from baseline was significantly greater for albuterol compared to metaproterenol (29.3% vs 20.6%; P<0.05). There were no significant differences in the mean change from baseline in systolic blood pressure in either group, however with metaproterenol the chronotropic effect was significantly greater (P<0.05) at 1 hour on day 1 and 28 and 1.5 hour on day 28 compared to albuterol. There was no significant difference in the frequency of adverse effects between the two groups (no P value reported). Secondary: Not reported
Salpeter et al[33] LABAs (formoterol via DPI) vs placebo	MA, 19 DD, PC, RCT Individuals diagnosed with asthma, 15% of the participants were African American	N=33,826 All trials were at least 3 months	Primary: Severe asthma exacerbations requiring hospitalizations, life-threatening asthma exacerbations, asthma-related deaths Secondary: Not reported	Primary: LABAs (formoterol and salmeterol) when compared with placebo resulted in an increase in severe exacerbations that required hospitalization (OR, 2.6; 95% CI, 1.6 to 4.3), life-threatening exacerbations (OR, 1.8; 95% CI, 1.1 to 2.9), and asthma-related deaths (OR, 3.5; 95% CI, 1.3 to 9.3), with similar risks seen in adults and children. Secondary: Not reported
Boonsawat et al[34] Formoterol 18 µg administered at 0, 30, and 60 minutes via DPI	DB, DD, PG, RCT Individuals 18 to 67 years old with asthma presenting	N=88 1 day	Primary: FEV_1, asthma symptoms	Primary: A non-significant increase in FEV_1 at 75 minutes compared to baseline was seen (37% in the formoterol group vs 28% in the albuterol group; P=0.18).

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vs albuterol 100 µg administered at 0, 30, and 60 minutes via MDI	to the ED with acute bronchoconstriction		Secondary: Not reported	There was a significant increase in the maximum FEV_1 between 75-240 and 15-45 minutes after the first and second dose of the medications in the formoterol group compared to the albuterol group (51% vs 36%; *P*<0.05). Subjective symptom score assessments decreased during the course of the study (no *P* value reported). Secondary: Not reported
Pauwels et al[35] Formoterol 4.5 µg administered as needed via DPI vs albuterol 200 µg administered as needed via MDI	MC, OL, RCT Individuals ≥6 years old with a diagnosis of asthma requiring the use of β_2-agonists as reliever medication	N=18,124 6 month	Primary: Asthma-related and non-asthma-related serious adverse events, and discontinuation due to adverse events, and time to first exacerbation Secondary: Rescue reliever mediation	Primary: The number of adverse effects reported was not statistically significant between the two groups (no *P* value reported). With formoterol there was a significantly higher number of asthma-related discontinuation due to adverse events (1.0% vs 0.5%; *P*<0.001). Compared with albuterol, there was a significantly longer time to first asthma exacerbation with formoterol (*P*<0.001). Secondary: Rescue inhaler use decreased in both groups over the course of the study with a significantly greater decrease seen in the formoterol group (*P*<0.001).
Molimard et al[36] Formoterol 12 µg via DPI and albuterol via MDI to use as needed (administered as separate products) vs albuterol 100 µg via MDI to be used	MC, OL, PG, RCT Individuals ≥18 years old with moderate persistent asthma	N=259 3 months	Primary: The mean change in morning predose PEF for the entire treatment period Secondary: Mean increase in evening predose PEF for the entire treatment period, and day and night	Primary: Over the 3 months there was a significantly higher mean increase in the morning PEF in the formoterol group than in the albuterol group (+25.7 L/min and 4.5 L/min (*P*<0.0001). Secondary: At visits 3 and 5 there was a significantly greater improvement in predose FEV_1 with formoterol compared to albuterol (*P*<0.01, *P*<0.05). At the conclusion of three months, the mean changes from baseline in the number of puffs of albuterol during the day and night were -0.8 and -0.4 with formoterol and +0.1 and +0.1 for albuterol (*P*<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
throughout the day as needed			use of albuterol and scores on the SGRQ	There was a significantly higher increase in symptom-free days and nights in the formoterol group when compared to albuterol (+20%, +30%; *P*<0.0001, *P*<0.003). A significantly higher decrease was seen in the SGRQ score with formoterol (-6.4) compared to albuterol (-3.5) (*P*=0.05).
Pleskow et al[37] Formoterol 12 µg BID via DPI vs formoterol 24 µg BID via DPI vs albuterol 180 µg QID via MDI vs placebo	DB, DD, MC, PC, PG, RCT Individuals 12 to 75 years old with mild to moderate asthma	N=554 12 weeks	Primary: FEV_1 at the 12-hour evaluation time point Secondary: AUC of FEV_1, and percent of predicted FEV_1	Primary: On the final visit at the 12-hour mark both formoterol groups showed significant improvement in FEV_1 compared to placebo and albuterol (*P*<0.001, *P*<0.002) with no statistical difference between albuterol and placebo at this time. Secondary: Overall, at the last visit, both formoterol groups showed significant improvement at all time points vs placebo (*P*<0.001) with the exception of formoterol 12 µg at time 0. Both groups also showed significant improvement against albuterol at time 0, 2-6 hours, and 10-12 hours (*P*<0.001, *P*<0.002). In the albuterol group there were also a significant difference compared to placebo at all points in time except 0, 4-6 and 10-12 hours (*P*<0.013). The AUC of FEV_1 was significantly different in favor of both formoterol groups compared to placebo (*P*<0.001), formoterol 24 µg compared to albuterol (*P*<0.001) and albuterol compared to placebo (*P*<0.008) at all visits. Both medications were well tolerated with no significant difference between them (no *P* value reported).
Bouros et al[38] Formoterol 12 µg BID via DPI, added to current beclomethasone DPI treatment (500 µg DAILY; administered	MC, OL, PG, RCT Individuals ≥18 years old who were symptomatic on 500 µg daily of inhaled beclomethasone	N=132 12 weeks	Primary: Mean PEF during final 7 days of treatment Secondary: Overall PEF, asthma symptoms,	Primary: There was a treatment effect of 20.36 L/min in the combination group over the patients receiving the double dose of steroid (*P*=0.021). Secondary: For the entire treatment period, the combination group had an overall evening premedication PEF that was significantly higher compared to the double dose of steroid (*P*<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
as separate products) vs beclomethasone 1,000 µg DAILY via DPI			rescue medication, and safety	There was a decrease in day and night symptom scores in both groups but there was a significant difference in favor of the combination treatment arm (night *P*=0.001, day *P*<0.001). In both groups the number of puffs of rescue medication taken decreased during the study, with a significant improvement seen with the combination compared to the double dose of the steroid (night *P*=0.003, day *P*<0.001). There was no significant difference in adverse events in either group (no *P* value reported).
Tinkelman et al[39] Metaproterenol via MDI vs pirbuterol via MDI	DB, MC, PG Asthmatic patients	N=133 12 weeks	Primary: Onset of action, peak effect, side effects, and tolerance Secondary: Not reported	Primary: There was no clinical difference between the two treatment groups in the outcomes (no *P* value reported). Secondary: Not reported
Von Berg et al[40] Salmeterol 50 µg BID via DPI vs placebo Both groups received albuterol MDI to use as needed.	DB, PC, PG, RCT Individuals 6 to 15 years old with a documented history of reversible airway obstruction requiring β_2-agonist treatment for symptomatic control	N=426 12 months	Primary: Change from baseline in mean morning PEF Secondary: Percent of symptom-free nights and days, percent of nights and days with no rescue inhaler, and incidence of asthma exacerbations	Primary: Over the first 6 months of the study, the adjusted mean change above baseline in mean morning PEF was 341 minutes in patients treated with salmeterol compared with 171 minutes for placebo (*P*<0.001). This significant improvement was maintained throughout the second 6 months of the study (*P*=0.03). Over the first 6 months of the study, the adjusted mean change above baseline in mean evening PEF was 251 minutes in patients treated with salmeterol compared with 121 minutes for placebo (*P*<0.001). This significant improvement was maintained throughout the second 6 months of the study (*P*=0.05). Secondary: Although the number of symptom-free days was high (86%) in both groups, there was no statistically significant difference between the treatment groups (no *P* value reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				There was a higher frequency distribution of the percentage of nights with no rescue inhaler use in patients receiving salmeterol compared to placebo that was significant throughout the 12-month treatment period (*P*<0.05). During the 12-month treatment period there was no statistically significant difference between the treatment groups in the number of patients with asthma exacerbations (*P*=0.2).
Nelson et al[41] Salmeterol 42 µg BID via DPI vs placebo Both groups received this treatment as a supplement, not a replacement to current treatment.	DB, MC, OS, PC, PG, RCT Individuals ≥12 years old with a diagnosis of asthma and currently using asthma medications	N=26,355 28 weeks	Primary: Occurrence of combined respiratory related deaths or respiratory related life-threatening experiences Secondary: All-cause deaths, combined asthma-related deaths or life-threatening experiences, asthma-related deaths, respiratory-related deaths, combined all-cause deaths or life-threatening experiences, and all-cause hospitalizations	Primary: There were 3 asthma-related deaths and 22 combined asthma-related deaths or life-threatening experiences in subjects receiving placebo compared to 13 asthma-related deaths and 37 combined asthma-related deaths or life-threatening experiences in subjects receiving salmeterol, a difference that was statistically significant (*P*<0.05). Secondary: There was no statistically significant difference seen in Caucasians in the primary or secondary end points (no *P* value reported). For the primary and two of the secondary end points there was a statistically significant difference in African Americans receiving salmeterol compared to placebo (*P*<0.05). Between the treatment groups there was a statistically significant difference for time to first serious adverse event causing discontinuation (placebo survival rate, 96.18%; salmeterol survival rate, 95.61%; *P*=0.022).
Boulet et al[42] Salmeterol 50 µg BID via DPI	DB, MC, PG, RCT, Individuals ≥12 years old	N=228 15 weeks	Primary: FEV_1	Primary: Salmeterol treatment resulted in a significantly greater mean improvement in FEV_1 compared with albuterol treatment from hours 3-6 (*P*<0.001) and 10-12 (*P*<0.012) and this effect was maintained

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs albuterol 200 µg QID via MDI	diagnosed with mild to moderate asthma requiring daily pharmacotherapy for at least 6 months		Secondary: PEF, symptoms, use of rescue medication, adverse events	throughout the study. Secondary: A significant improvement in evening PEF was seen for salmeterol treated patients compared to albuterol (34 L/min vs 6 L/min; *P*<0.001). The average percent increase of symptom free days in the salmeterol group was significantly greater than albuterol (29% vs 15%; *P*=0.012). There was no significant difference in rescue medication use between the two groups and both treatments were well tolerated (no *P* value reported).
Faurschou et al[43] Salmeterol 100 µg BID via DPI and as needed albuterol vs albuterol 400 µg QID via MDI and as needed albuterol All patients continued to receive their inhaled corticosteroid dose.	DB, DD, MC, PG, RCT Individuals ≥18 years old with chronic asthma currently receiving inhaled corticosteroids	N=190 6 weeks	Primary: PEFR Secondary: Symptom scores, use of rescue inhaler, FEV_1, and patient and physician assessment of efficacy	Primary: The mean morning PEFR improved by 33 L/min in the salmeterol group compared to 4 L/min in the albuterol group at the conclusion of the study. This difference was statistically significant (*P*<0.001). There was a significant reduction in diurnal variation in the salmeterol group, from 39 L/min to 22 L/min compared to the albuterol group with a change from 34 L/min to 37 L/min (*P*<0.001). Secondary: Salmeterol increased FEV_1 after 3 and 6 weeks compared to baseline significantly more than albuterol (*P*<0.05 for both weeks). There was a significant improvement in symptom-free nights in the salmeterol group compared to the albuterol group *(P*<0.001); however, there was no significant difference in symptom-free days. There was no difference in the number of rescue-free days between the groups; however, there was an increase in percent of rescue-free nights in the salmeterol-treated group (*P*<0.04).
Vervloet et al[44] Salmeterol 50 µg BID via DPI	MC, OL, PG, RCT Individuals ≥18 years old in the outpatient setting	N=482 6 months	Primary: Mean morning predose PEF during the last 7 days of treatment	Primary: The 95% CI for the treatment contrast formoterol minus salmeterol was -8.69, +9.84 L/min during the last 7 days of treatment and was included entirely in the predefined range of equivalence (no *P* value reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs formoterol 12 µg BID via DPI	with moderate to severe reversible obstructive airway disease for at least 1 year and currently using regular inhaled corticosteroids (no attempt was made to exclude patients with COPD)		Secondary: Mean morning and evening predose PEF during the last week before each clinic visit, overall mean morning and evening pre-dose PEF, day and night use of rescue medication and time symptoms score	Secondary: The estimated treatment contrasts showed a trend towards greater efficacy with formoterol over salmeterol for mean evening predose PEF, which became statistically significant at 2, 3, and 4 months (P<0.05). Both treatments resulted in a mean decrease in rescue medication use to less than half compared to baseline and an improvement in mean symptom score but no significant difference between the groups was found (no P value reported). Both medications were found to be safe and well tolerated (no P value reported).
Condemi et al[45] Salmeterol 50 µg BID via DPI vs formoterol 12 µg BID via DPI	AC, MC, PG, OL Individuals 18 to 75 years old with moderate to moderately severe asthma diagnosed at least 1 year prior and currently on inhaled corticosteroids	N=528 6 months	Primary: Mean morning PEF measured 5 minutes after dosing Secondary: Mean morning and evening predose PEF, number of episode-free days, use and time of rescue medications, symptom score, overall mean morning predose PEF, and safety	Primary: There was a significant increase in mean PEF values measured 5 minutes after dosing in patients receiving formoterol compared to salmeterol (393.4 L/min vs 371.7 L/min; P<0.001). Secondary: Individuals receiving formoterol reported using significantly fewer actuations of rescue medication per week within 30 minutes of dosing (1.4 vs 2.1; P<0.005), significantly fewer actuations between morning and evening doses (5.6 vs 7.7; P<0.03) and significantly fewer actuations between evening and morning doses (2.8 vs 4.2; P<0.03) all compared to salmeterol. Patients experienced significantly more episode free days in the formoterol group compared to salmeterol (9.5 vs 7.8; P<0.04). Mean morning predose PEF, mean evening predose PEF and nighttime or daytime symptom scores did not differ significantly between treatments (no P value reported).
Condemi[58] Formoterol 12 µg BID via DPI	MC, OL, PG, RCT Patients 18 to 75 years old diagnosed with	N=528 6 months	Primary: Mean morning PEF measured 5 minutes after administration of study medication	Primary: There was a significant improvement in mean PEF measured 5 minutes after administration of study medication in patients in the formoterol group compared to the salmeterol group (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs salmeterol 50 µg BID via DPI	moderate to moderately severe asthma for at least 1 year prior to screening, receiving low-dose inhaled corticosteroids for at least 1 month, requiring SABA >4 times per week, FEV_1 of 40%-80% of predicted value, >12% improvement in FEV_1 after use of a SABA		during the first 4 weeks of treatment Secondary: Mean morning and evening pre-dose PEF, number of episode-free days, use of rescue medications, symptom scores (all during the first 4 weeks of treatment), and mean overall morning pre-dose PEF	Secondary: There was no significant difference in mean morning and evening pre-dose PEF values during the first 4 weeks of the study or mean morning pre-dose PEF for the entire study period between the formoterol and salmeterol groups (*P* values not reported). There was a significant reduction in the use of rescue medication in the formoterol group compared to the salmeterol group (*P*<0.03). There was a significant increase in episode free days in the formoterol group compared to the salmeterol group (*P*<0.04).
Brambilla et al[46] Salmeterol 50 µg BID via DPI and as needed albuterol vs formoterol 12 µg BID via DPI and as needed albuterol vs as needed albuterol All patients continued to receive their inhaled corticosteroid dose.	MC, OL, PG, RCT Individuals ≥18 years old with moderate to severe persistent asthma sub-optimally controlled on inhaled corticosteroids with on demand albuterol with or without salmeterol	N=6,239 4 weeks	Primary: Difference in evening predose PEF between patients continued on salmeterol and these switched to formoterol Secondary: Morning predose PEF, daytime and nighttime asthma symptom score, use of rescue inhaler, percent days with no asthma symptoms or albuterol use	Primary: A significant increase in mean evening predose PEF was seen in patients switched to formoterol from salmeterol or albuterol as needed compared to patients staying on salmeterol (402.9 vs 385.5 L/min; *P*<0.001) and albuterol as needed (409.3 vs 385.0 L/min; *P*<0.001). Secondary: In patients switched to formoterol compared to individuals who continued to receive salmeterol or on-demand albuterol there was a significant increase in morning predose PEF, a significantly reduction in both daytime and nighttime asthma symptom score, a significant higher percent of symptom free days, a significant reduction in rescue medication use (all *P*<0.001). There was no significant difference in the incidence of adverse effects between treatment groups (no *P* value reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Martin et al[47] Salmeterol 42 µg two inhalations BID via DPI vs albuterol extended release tablets 4 mg in the morning and 8 mg in the evening	DB, DD, MC, RCT, XO Individuals 18 to 65 years old with FEV_1>50% and 12% improvement following inhaled albuterol	N=56 8 weeks	Primary: Morning peak flow, FEV_1 measurements Secondary: Nocturnal symptoms, nights without awakenings, rescue inhaler use, safety analysis	Primary: Improvements in PEF and FEV_1 were both significantly improved in bother treatment groups (*P*<0.001) but did not differ significantly between themselves (no *P* value reported). Secondary: A comparison of the adjusted treatment means for the percentage of nights without awakenings demonstrated a significant improvement with salmeterol (84.6 vs 79.4; *P*=0.021). There was no statistical difference between the two groups concerning the percentage of patients who had no nocturnal awakenings (no *P* value reported). A significant decrease in baseline puffs per day of a rescue inhaler was observed in both the salmeterol (4.57 to 1.85; *P*<0.001) and the extended release albuterol tablets (4.57 to 2.66; *P*<0.001). The decrease with salmeterol was significantly greater (*P*<0.001). 78.0% of the patients treated with extended release albuterol tablets and 75.9% of patients treated with salmeterol listed adverse effects during the study. A difference that was not statistically significant (no *P* value reported).
Brambilla et al[48] Salmeterol 50 µg BID via DPI vs terbutaline sustained release 5 mg tablets BID	DB, DD, MC, PG, RCT Individuals 18 to 67 years old suffering from chronic asthma with greater than 15% reversibility after inhaled albuterol	N=159 2 weeks	Primary: Number of awakening-free nights over the last week of treatment Secondary: Morning PEF, evening PEF, PEF diurnal variations, and nocturnal and diurnal rescue albuterol intake	Primary: In the salmeterol group the mean number of awakening-free nights over the last week of treatment was significantly higher than with the terbutaline sustained release (5.3 vs 4.6; *P*=0.006). Secondary: No significant difference was found concerning the mean evening PEF; however, salmeterol was more efficacious than terbutaline sustained release on morning PEF (*P*=0.04) and PEF daily variations (*P*=0.01). A significantly greater percent of individuals in the salmeterol group (30%) compared to the terbutaline group (9%) stopped using rescue albuterol during the day (*P*=0.004), but there was no significant

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				difference at night (no *P* value reported). Significantly fewer patients in the albuterol group reported adverse events (16% vs 29%; *P*=0.04).
Estelle et al[49] Salmeterol 50 µg BID via DPI vs beclomethasone 200 µg BID via DPI vs placebo	DB, PC, PG, RCT Individuals 6 to 14 years old with stable asthma	N=241 56 weeks	Primary: Airway hyper-responsiveness Secondary: PEF, rescue inhaler use, and adverse effects	Primary: During months 1-2 of the study there was significantly less airway hyperresponsiveness with beclomethasone when compared with salmeterol (*P*=0.003) or placebo (*P*<0.001), however this difference was lost 2 weeks after discontinuation of treatment. Secondary: In the beclomethasone group the PEF varied significantly less when compared to the salmeterol and placebo groups (*P*=0.002, *P*=0.02) with the similar effects seen with beclomethasone and salmeterol. Compared to the placebo group, individuals receiving beclomethasone required significantly less rescue medication and had fewer withdrawals due to exacerbations (*P*<0.001, *P*=0.03); however, the difference between salmeterol and placebo was not significant (no *P* value reported). Height in the beclomethasone-treated children increased by 3.96 cm during months 1-12, which was significantly less than the height increase in the placebo-treated children (5.04 cm; *P*=0.018) and the salmeterol-treated children (5.40 cm; *P*=0.004).
Lazarus et al[50] Salmeterol 42 µg BID via MDI vs triamcinolone 400 µg BID via MDI vs	DB, MC, PC, PG, RCT Individuals 12 to 65 years old with persistent asthma	N=164 28 weeks	Primary: Change in morning PEF from the final week of the run in period to the final week of treatment Secondary: FEV_1, asthma symptom scores, rescue albuterol	Primary: No significant difference in morning PEF measures was seen between the treatment groups; however, they were both more effective compared to placebo (no *P* values reported). Secondary: There was no significant difference between the salmeterol and triamcinolone groups in terms of asthma symptom scores, rescue inhaler use, or quality of life; both treatment arms were more effective compared to placebo in these categories (no *P* values reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo			use, quality of life scores, and number of exacerbations	There were significantly more group treatment failures in the salmeterol group than the triamcinolone (25% vs 6%; *P*=0.004) as well as more exacerbations (20% vs 7%; *P*=0.04).
Tattersfield et al[51] Terbutaline 0.5 mg as needed via DPI vs formoterol 4.5 µg as needed via DPI	DB, PG, RCT Individuals ≥18 years old with asthma for at least six months and treated with a constant dose of inhaled corticosteroid for at least 4 weeks	N=362 12 weeks	Primary: Time to first severe exacerbation Secondary: Morning and evening peak flow rate, FEV_1, symptoms, number of inhalations of relief medication, and safety data	Primary: In the formoterol group, patients experienced a longer time to the first severe exacerbation than in the terbutaline group (*P*=0.013) with the relative risk ratio for having an exacerbation first in the formoterol group compared with terbutaline group of 0.55. Secondary: No significant difference was seen between the treatment groups concerning daytime or nighttime symptoms (no *P* value reported). It was documented that pre-bronchodilator FEV_1 was greater in the formoterol group than terbutaline (no *P* value reported). Both treatment groups experienced a decrease in rescue inhalations but it was to a greater extent in the formoterol group (1.15 vs 0.40; no *P* value reported). Both treatments were well tolerated.
Hermansson et al[52] Terbutaline 500 µg QID via DPI vs salmeterol 50 µg BID via DPI	MC, OL, PG, RCT Individuals ≥18 years old with mild to moderate asthma	N=243 4 weeks	Primary: Morning, evening and diurnal PEF, daytime and nighttime symptoms, use of rescue inhaler, FEV_1 Secondary: Not reported	Primary: Over 4 weeks salmeterol produced significant improvements over terbutaline in morning and evening PEF and diurnal variation (*P*<0.001, *P*=0.045, *P*<0.001). After 4 weeks there was a statistically significant difference in favor of the salmeterol group in daytime and nighttime asthma score, and percent of days and nights when a rescue medication was needed (*P*<0.001, *P*=0.008, *P*=0.002, *P*=0.007). After 4 weeks of treatment there were no significant differences in FEV_1 or FVC between the two groups (*P*=0.598, *P*=0.916). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Hancox et al[53] Terbutaline 1,000 µg QID via DPI vs budesonide 400 µg BID via DPI vs terbutaline 1,000 µg QID and budesonide 400 µg BID via DPI vs placebo	PC, RCT, XO Individuals aged 9 to 64 years old with mild to moderate asthma with documented hyper-responsiveness	N=61 24 weeks	Primary: Construct a rank order of treatment from worst [1] to best [4], period of asthma control for each subject Secondary: PEF, nocturnal and daytime symptoms, use of rescue medication, and compliance	Primary: Combined treatment was ranked significantly higher than each individual treatment and placebo (P<0.0001, P<0.0001, and P<0.01), budesonide ranked higher than placebo (P=0.025), and there was no significant difference between budesonide and terbutaline or terbutaline and placebo. Secondary: Mean morning peak flow was higher during combined treatment than budesonide alone (P<0.02), and both the combined treatment and budesonide were higher then either placebo or terbutaline (P<0.01). Mean evening peak flow was higher with all treatments (P<0.0003) and was higher with the combined treatment than either active medication alone (P<0.0002), but no significant difference was seen between the two active medications alone. Nocturnal awakenings and percent of days during which wheeze was reported were reduced significantly in all treatment groups compared with placebo (P<0.0001, P<0.001), but did not differ significantly between the treatment groups. Rescue inhaler use significantly decreased in all treatment groups compared with placebo (P<0.001), but did not differ significantly between the treatment groups. The self-reported compliance was above 90% for all groups and did not differ significantly (no P value reported).
Chronic Obstructive Pulmonary Disease				
Baumgartner et al[54] Arformoterol 15 µg BID via nebulizer vs arformoterol 25 µg BID	DB, MC, PC, RCT Men and women ≥35 years old with primary diagnosis of COPD and FEV_1 ≤65% predicted and >0.70 L, with	N=717 12 weeks	Primary: Mean percentage change from baseline in morning trough FEV_1 averaged over 12-weeks	Primary: Patients taking all three doses of arformoterol BID and salmeterol BID experienced statistically significant improvements in morning trough FEV_1 throughout 12 weeks of daily treatment compared to placebo (P<0.001). Secondary: Arformoterol 15 µg BID demonstrated significantly greater improvement

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
via nebulizer vs arformoterol 50 µg DAILY via nebulizer vs salmeterol 42 µg BID via MDI vs placebo Patients were allowed to use albuterol MDI as a rescue therapy and ipratropium MDI as a supplemental medication as needed.	Medical Research Council Dyspnea Scale Score ≥2 and FEV_1/FVC ratio ≤70%, a minimum smoking history of 15 pack-years at baseline		Secondary: Percent change in from baseline in 12-hour FEV_1 AUC averaged over time 0 to 12 hours after study drug administration.	in the percent change from pre-dose in the 12-hour FEV_1 $AUC_{0\text{-}12\ h}$ versus placebo (P<0.001). Greater improvement in FEV_1 $AUC_{0\text{-}12\ h}$ was also observed for the arformoterol group compared to salmeterol over the 12 week period (P<0.024). Compared with 15 µg BID, higher doses did not provide sufficient additional benefit to support their use. Adverse events of the three doses of arformoterol were similar compared to salmeterol and placebo. The most serious adverse events were of respiratory and cardiovascular in nature.
Data on file[55] arformoterol 15 µg BID via nebulizer vs arformoterol 25 µg BID via nebulizer vs arformoterol 50 µg DAILY via nebulizer	DB, PC, MC, RCT Men and women ≥35 years old with primary diagnosis of COPD and FEV_1 ≤65% predicted and >0.70 L, with Medical Research Council Dyspnea Scale Score ≥2 and FEV_1/FVC ratio ≤70%, a minimum smoking history of	N=739 12 weeks	Primary: Mean percentage change from baseline in morning trough FEV_1 averaged over 12-weeks Secondary: Percent change in from baseline in 12-hour FEV_1 AUC averaged over time 0 to 12 hours after	Primary: Patients taking arformoterol BID and salmeterol BID experienced statistically significant improvements in morning trough FEV_1 throughout 12 weeks of daily treatment (P<0.001). Secondary: Arformoterol 15 µg BID demonstrated significantly greater improvement in the percent change from predose in the 12 hour FEV_1 $AUC_{0\text{-}12\ h}$ versus placebo (P<0.001). Adverse events of the three doses of arformoterol were similar compared to salmeterol and placebo.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs salmeterol 42 µg BID via MDI vs placebo Patients were allowed to use albuterol MDI as a rescue therapy and ipratropium MDI as a supplemental medication as needed.	15 pack-years at baseline.		study drug administration	
Benhamou et al[56] Formoterol 24 µg via DPI (1 dose) vs albuterol 400 µg inhaled via DPI (1 dose) vs placebo	DB, PC, RCT, XO Individuals 40 to 75 years old with stable, reversible COPD	N=25 1 dose	Primary: AUC (0-30 min) of FEV_1 in 1 minute Secondary: AUC (0-1 hour) of FEV_1 in 1 minute, AUC (0-3 hours) of FEV_1 in 1 minute, maximal change in FEV_1 a percent of predicted value	Primary: There were no significant differences between formoterol (5.89) and salmeterol (6.06) in primary endpoint, but both were statistically higher than placebo (-0.32; *P*<0.0001). Secondary: There were no statistical differences between the two active medication groups in secondary endpoints, and each had a similar onset (5 minutes; no *P* value reported). No serious adverse effects or clinically relevant changes in vital sign were observed in any of the groups (no *P* value reported).
Cazzola et al[57] Formoterol 12 µg, 12 µg, and 24 µg via DPI vs	RCT, SB, XO Patients 51 to 77 years old diagnosed with COPD, having an acute exacerbation	N=16 2 days	Primary: Maximum FEV_1 value during the dose-response curve Secondary:	Primary: There was a significant increase in FEV_1, IC, and FVC in both the albuterol and formoterol groups compared to baseline after 48 µg of formoterol and 800 µg of albuterol (*P*<0.05). There was no significant difference between FEV_1, IC, and FVC values in the formoterol group compared to the albuterol group after 48 µg of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
albuterol 200 µg, 200 µg, and 400 µg via MDI Doses administered on two consecutive days.	of COPD defined as sustained worsening of the patient's condition from stable and beyond normal day-to-day variations, FEV_1 <70% of personal best that is acute in onset and necessitating a change in the medication regimen		Spirometric data (IC and FVC), pulse rate, SpO_2 values	formoterol and 800 µg of albuterol. There was a significant increase in change in FEV_1 values after 24 µg of formoterol compared to 48 µg of formoterol (*P*=0.022). There was no significant difference in pulse rate or SpO_2 values compared to baseline after 48 µg of formoterol or 800 µg of albuterol (*P*>0.05). SpO_2 values decreased below 90% in 2 patients after the highest dose of formoterol and in 1 patient after the highest dose of albuterol. The clinical significance of this finding was not reported.
Datta et al[59] Levalbuterol 1.25 mg via nebulizer vs albuterol 2.5 mg via nebulizer vs albuterol/ipratropium 2.5 mg/0.5 mg via nebulizer (administered as a combination product) vs placebo	DB, RCT, XO Patients with diagnosis of COPD, mean age of 69 years, FEV_1 45%-75% of predicted value, FEV_1/FVC ratio of <0.70, stable disease (absence of clinical exacerbation and no change in COPD medications in previous month), and the ability to withhold bronchodilator medications for the washout period prior to each	N=30 4 days	Primary: FEV_1 Secondary: FVC, pulse rate, oxygen saturation (measured by pulse oximetry), hand tremor (rating scale 0-7, rated by same blinded investigator for all patients)	Primary: Mean change in FEV_1 from baseline increased significantly in all 3 active treatment groups compared to placebo at 0.5 hours and persisted at 1 hour (*P*<0.05). At 2 hours, only the combined albuterol and ipratropium group had a mean change in FEV_1 that was significantly better than placebo (*P*=0.04). This effect persisted at 3 hours for the combined albuterol and ipratropium group (*P*<0.05). There were no significant differences between active treatment groups at any time during the study (no *P* value reported). The percentage of patients in exhibiting a positive bronchodilator response (defined as both a >12% increase and a 0.20 L increase in FEV_1) was significantly increased in all 3 active treatment groups compared to placebo at 0.5 hours ($P \leq 0.03$) and this persisted at 1 hour ($P \leq 0.03$). The percentage of patients in exhibiting a positive bronchodilator response at 2 and 3 hours was only significant compared to placebo in the combined albuterol and ipratropium group (*P*=0.03 at 2 hours and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	testing			*P*=0.003 at 3 hours). Between-group comparisons were not reported. Secondary: All 3 active treatment groups led to significant improvements in FVC compared to placebo at 0.5 hours (*P*<0.05) and remained significant at 1 hour only for the combined albuterol and ipratropium group (*P*<0.05). No significant differences between active treatment groups and placebo were noted from 2 hours on (no *P* values reported). Differences in FVC between active treatment groups were similar (no *P* values reported). Significant increases in pulse rate compared to placebo were noted at 0.5 hours in the albuterol and levalbuterol groups (*P*<0.01) but no differences were noted at 1 hour and beyond. No significant changes in oxygen saturation were noted in any group compared to placebo (no *P* values reported). No significant differences in hand tremor noted between groups (no *P* values reported).
Hanania et al[60] Fluticasone 250 µg BID via DPI vs salmeterol 50 µg BID via DPI vs fluticasone/salmeterol 250/50 µg BID via DPI (administered as a	DB, MC, PC, RCT Patients 40 to 87 years old, current or former smokers with ≥20 pack year history, diagnosed with COPD, FEV_1/FVC ratio of ≤70%, baseline FEV_1 of <65% predicted normal value but >0.70 L (or if ≤0.70 L, then >40% predicted)	N=723 24 weeks	Primary: Morning pre-dose FEV_1 and 2 hour post-dose FEV_1 Secondary: Morning PEF values, transition dyspnea index, CRDQ, CBSQ, exacerbations, and supplemental albuterol use	Primary: Statistically significant increase in pre-dose FEV_1 in fluticasone/ salmeterol group compared to the salmeterol group (*P*=0.012) and placebo (*P*<0.001). No significant difference between fluticasone/ salmeterol group and fluticasone group. Statistically significant increase in 2 hour post-dose FEV_1 in fluticasone/ salmeterol group compared to the salmeterol group (*P*<0.001), placebo (*P*<0.001), and fluticasone group (*P*≤0.048). Secondary: Statistically significant increase in morning PEF values in fluticasone/ salmeterol group compared to the salmeterol group, placebo group, and fluticasone group (*P*≤0.034), though improvements were also seen from baseline in salmeterol and fluticasone monotherapy groups (*P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
combination product) vs placebo				Statistically significant improvements in dyspnea index observed in fluticasone/salmeterol group (*P*=0.023) compared to placebo, in addition to improvements in fluticasone (*P*=0.057) and salmeterol (*P*=0.043) monotherapy groups compared to placebo. Statistically significant reduction in supplemental albuterol use in fluticasone/salmeterol group compared to fluticasone monotherapy group (*P*=0.036) and placebo (*P*=0.002). Numerical reduction in supplemental albuterol use in fluticasone/ salmeterol group compared to salmeterol monotherapy group. Statistically significant increase in CRDQ scores in fluticasone/ salmeterol group compared to placebo (*P*=0.006). Statistically significant increase in CRDQ scores in fluticasone monotherapy group compared to placebo (*P*=0.002). Statistically significant increase in CBSQ scores in fluticasone/ salmeterol group and fluticasone monotherapy group compared to placebo (*P*≤0.017).
Lee et al[61] Exposure to inhaled corticosteroids, ipratropium, LABAs, theophylline, and SABAs	Nested case-control Patients treated in the United States Veterans Health Administration health care system	N=145,020 Cohort identified between October 1, 1999 and September 30, 2003 and followed through September 30, 2004	Primary: All-cause mortality, respiratory mortality, cardiovascular mortality Secondary: Subgroup analyses of primary outcomes	Primary: After adjusted for differences in covariates, inhaled corticosteroids and LABAs were associated with reduced odds of death. An adjusted OR of 0.80 (95% CI, 0.78 to 0.83) for inhaled corticosteroids and 0.92 (95% CI, 0.88 to 0.96) for LABAs was observed. Ipratropium was associated with an increased risk of death (OR, 1.11; 95% CI, 1.08 to 1.15). Theophylline exposure was associated with a statistically significant increase in respiratory deaths compared with the unexposed group (OR, 1.12; 95% CI, 1.46 to 2.00). An increase in the odds of respiratory death was observed with LABAs (OR, 1.12; 95% CI, 0.97 to 1.30), however the increase did not reach statistical significance. In addition, a decrease in the odds of respiratory death was observed with inhaled corticosteroids (OR, 0.88; 95% CI, 0.79 to 1.00), however this also did not reach statistical significance.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Exposure to ipratropium was associated with a 34% increase in the odds of cardiovascular death (OR, 1.34; 95% CI, 0.97 to 1.47), whereas inhaled corticosteroids exposure was associated with a 20% decrease (OR, 0.80; 95% CI, 0.72 to 0.88). LABAs (OR, 0.97; 95% CI, 0.99 to 1.37) and theophylline (OR, 1.16; 95% CI, 0.99 to 1.37) were not associated with statistically significant risks in cardiovascular deaths. Secondary: In a sensitivity analysis based on dose of medication, higher doses were associated with a larger effect than lower doses, consistent with a dose response to the medication. With current smoking associated with a RR for death of 1.5, these estimates would result in adjusted risk ratios of 0.77 for inhaled corticosteroids, 1.08 for ipratropium, and 0.90 for LABAs. Among the medication regimens, those that included theophylline were associated with increased risk for respiratory death. For cardiovascular death, ipratropium alone (OR, 1.42; 95% CI, 1.27 to 1.59) and ipratropium plus theophylline (OR, 1.47; 95% CI, 1.09 to 1.98) were associated with increased risk, whereas the presence of inhaled corticosteroids with ipratropium reduced the risk for cardiovascular death (OR, 1.04; 95% CI, 0.90 to 1.22; *P*<0.001). In the all-cause mortality group, inhaled corticosteroids were consistently associated with reduced odds of death when used alone or in combination with other medications, whereas ipratropium and ipratropium plus theophylline were associated with elevated risk for death.
Exercise-Induced Bronchospasm				
Berkowitz et al[62] Albuterol 0.18 mg, two inhalation 15 minutes prior to exercise via MDI	RCT, SB, XO Patients 12 to 17 years old with bronchial asthma and found to have	N=18 4 days	Primary: Mean percentage increase in FEV_1 five minutes after medication, mean workload for	Primary: Differences between mean baseline FEV_1 were not statistically significant between the treatment groups; however, five minutes post administration of albuterol or metaproterenol the mean increase in percentage of predicted FEV_1 was significantly higher compared with placebo (*P*<0.0005). A significantly greater increase (*P*<0.01) was also

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs metaproterenol 1.3 mg, two inhalation 15 minutes prior to exercise via MDI vs placebo	exercised-induced bronchospasm (FEV_1 of greater than 20% of pre-exercise level) following a treadmill exercise test		exercise challenges, mean decrease in FEV_1 from baseline, and the number of patients in whom broncho-constriction was blocked over time Secondary: Not reported	seen five minutes after the administration of metaproterenol when compared with albuterol. On the days when the subjects received the active medications, the mean workloads were not found to be significantly different. Following the initial post-medication exercise test, a majority of patients in the placebo group experienced exercise-induced spasm compared to both active ingredient groups. This was a significant difference (P<0.0005) between the placebo and active ingredient groups but not between the active ingredient groups themselves. Following the two-hour exercise challenge, the remainder of the placebo group experienced exercise-induced spasm and a greater number in the remaining metaproterenol group compared to the albuterol group experienced exercise-induced spasm. There was a greater decrease in mean maximum decrease in FEV_1 in the placebo group compared to the active ingredient groups, which was found to be statistically significant (P<0.001). Albuterol prevented exercise-induced bronchospasm in more patients and for a significantly longer time than metaproterenol did (P<0.05). Secondary: Not reported
Shapiro et al[63] Albuterol 180 µg prior to exercise challenge via MDI vs formoterol 12 µg prior to exercise challenge via DPI	DD, XO Individuals 12 to 50 years old with a baseline FEV_1 >70% and at least a 20% reduction in FEV_1 after 2 exercise challenges 4 hours apart	N=20 4 test sequences	Primary: Maximum percent decrease in FEV_1 after each exercise challenge Secondary: Length of coverage, rescue therapy, and tolerability	Primary: Both formoterol doses produced significantly greater inhibition of FEV_1 decrease compared to placebo at all points in time (P<0.01), and compared to albuterol at all points in time with the exception of 15 minutes post dose (P<0.01). The two formoterol dose groups were not statistically different from each other and the only point in time that the mean maximum percent decrease in FEV_1 with albuterol was statistically different from placebo was 15 minutes post dose (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs formoterol 24 µg prior to exercise challenge via DPI vs placebo				Secondary: 89%-94% of patients given formoterol and 79% of patients receiving albuterol were protected within 15 minutes of administration. Additionally, 71% of patients receiving formoterol were protected 12 hours after dosing compared to 26% of patients receiving albuterol, a percentage close to the 29% of patients receiving placebo (no *P* values reported). 19% of the patients treated with albuterol required a rescue inhaler at least once compared to 0 patients receiving formoterol (no *P* value reported). There was no statistical difference in the percent of patients experiencing adverse effects in all of the groups (no *P* value reported).
Richter et al[64] Formoterol 12 µg prior to exercise challenge via DPI vs salmeterol 50 µg prior to exercise challenge via DPI vs terbutaline 500 µg prior to exercise challenge via DPI vs placebo	DB, DD, PC, RCT, XO Non smoking patients 25 to 48 years old with mild to moderate asthma, a history of exercise-induced bronchoconstriction and a documented hyper-responsiveness to inhaled methacholine	N=25 13 visits	Primary: Percent increase in FEV_1 between the inhalation of the study medication and the initiation of exercise (5, 30, or 60 minutes), AUC of percent change in FEV_1 from end of exercise to 90 minutes Secondary: Not reported	Primary: At 5 minutes there was a significantly stronger response with terbutaline than salmeterol ($P<0.001$) and at 5, 15, 30, and 60 minutes after inhalation, formoterol provided greater bronchodilation than salmeterol ($P<0.05$). There was no significant difference between terbutaline and formoterol at any of the time points. Mean pre-exercise FEV_1 was significantly larger in all active medication groups compared with placebo at 30 and 60 minute intervals ($P<0.01$) and was significantly larger after terbutaline and formoterol compared to salmeterol and placebo at the 5-minute interval ($P<0.05$). A statistically significant ($P<0.01$) decrease was seen in AUC with increasing time between inhalation and exercise with terbutaline, formoterol, and salmeterol; however, there was no difference between treatments. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Edelman et al[65] Montelukast 10 mg orally once in the evening vs salmeterol 100 µg, two inhalations BID via DPI	DB, PG, RCT Patients 15 to 45 years old who had been nonsmokers for at least 1 years and had a smoking history of less than 15 pack-years; patients had a history of chronic asthma and a decrease in FEV_1 of at least 20% after a standardized exercise challenge on two occasions during the baseline period	N=191 8 weeks	Primary: Change from baseline in the maximal percentage decrease in FEV_1 at the end of 8 weeks of treatment Secondary: Change from baseline for maximal percent decrease in FEV_1 at days 1-3 and week 4, the time required after maximal decrease to return to within 5% of pre challenge values, AUC at all visits, the number and percent of patients requiring rescue medication during or at the conclusion of exercise test, and the number and percent of patients whose decrease in FEV_1 from pre-exercise levels was <10%, 10-20%, 20-40% and >40%	Primary: In both treatment groups spirometry before exercise resulted in a small, non-significant change from baseline FEV_1 at first treatment visit at weeks 4 and 8, the groups did not differ statistically (no *P* value reported). No statistical difference was seen at baseline in the maximal percent decrease in FEV_1. Improvement in maximal percent decrease in FEV_1 observed was maintained at week 8 for the montelukast group, compared to the salmeterol group (*P*=0.002). Secondary: No statistical difference was seen at baseline in the post exercise AUC or time to recovery within 5 minutes. Improvement in maximal percent decrease in FEV_1 was similar in both groups between days 1-3 and was maintained at week 4 in the montelukast group but not in the salmeterol group (*P*=0.015). A similar trend was also seen when evaluating the time required after maximal decrease to return to within 5% of pre challenge values and the AUC at all visits. The effect of salmeterol diminished while that of montelukast was maintained (*P*<0.001, *P*<0.001, *P*=0.010, *P*<0.001). 25 of 96 (26%) patients in the montelukast group required rescue doses of medication after exercise challenge at any post treatment visit compared to 37 of 93 (40%) in the salmeterol group, a difference that was statistically significant (*P*=0.044). After 8 weeks 62 of 93 (66.7%) of patients in the montelukast group achieved a decrease in FEV_1 of <20% after exercise challenging the salmeterol group compared to 41 of 90 (45.6%) of patients receiving salmeterol (*P*=0.028). Both medications were generally well tolerated.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Storms et al[66] Montelukast 10 mg orally DAILY in the evening vs salmeterol 50 µg BID via DPI vs placebo	DB, MC, PG, RCT Patients 15 to 45 years old at least a 1-year history of asthma, documentation of exercise-induced bronchospasm in the past year, and were uncontrolled on ICS for at least 2 months	N=122 4 weeks	Primary: Effect on the maximum FEV_1 after β_2-agonists administered to patients with 4 weeks of treatment with placebo, montelukast, or salmeterol Secondary: Effects of treatment on pre-exercise FEV_1, exercise exacerbation, rescue bronchodilation, time to recovery to pre exercise FEV_1 level and average CEAQ	Primary: The maximum post-rescue medication FEV_1 after 4 weeks improved in the montelukast and placebo group but not in the salmeterol group (+1.5%, +1.2% and -3.9%). This maximum FEV_1 was significantly less in the salmeterol group compared to the montelukast (*P*<0.001) and placebo group (*P*<0.001). Results were similar to those obtained after 1 week of therapy and the difference between the montelukast and placebo groups was not significant. Secondary: There was a significant improvement in the in the mean change from baseline in pre-exercise FEV_1in the salmeterol group compared to the placebo (at week 1; *P*<0.001) and montelukast group (at weeks 1 and 4; *P*=0.010). In addition, there was no difference between the montelukast and placebo groups. Montelukast significantly decreased EIB at week 4 compared to placebo (*P*=0.008), however, there was no significant difference between the salmeterol and placebo groups or the salmeterol and montelukast groups. Compared to both placebo and salmeterol, after 4 weeks of treatment montelukast permitted significantly faster rescue with β_2-agonists (*P*=0.036, *P*=0.005). After 4 weeks, there was a significant difference in the CEAQ score immediately and 10 minutes after exercise with montelukast compared to placebo (*P*<0.020). Both medications were generally well tolerated.
Miscellaneous Studies				
Huchon et al[67] Fenoterol/ipratropium via HFA134a-MDI (administered as a	MC, OL, PG, RCT Patients 18 to 80 years old with chronic airway	N=2,027 (HFA=1,348 CFC=679) 12 weeks	Primary: Adverse events Secondary: Additional use of the	Primary: The incidence of adverse events in the 2,027 randomized patients was comparable between the two treatment groups with 36.4% (N=491) in the HFA-MDI group and 37.1% (242) in the CFC-MDI group reporting at least one adverse event during the randomized phase.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
combination product) vs fenoterol/ipratropium CFC-MDI (administered as a combination product)	obstruction or mixed conditions as partly defined by the American Thoracic Society, stable chronic airway obstruction with no hospital admissions for an exacerbation and no major change in medication for at least 4 weeks prior to screening visit, an initial FEV_1 of ≥40% of the predicted value when not receiving a bronchodilator		study drug as rescue medication and the number of chronic airway obstruction exacerbations.	In addition, the rates of potential systemic effects of the trial drug, based on the incidence of cardiovascular events, mouth dryness or tremor, were balanced across both formulations. The most commonly reported adverse events were respiratory disorders including asthma or COPD exacerbations, bronchitis, cough, and dyspnea. There were no statistically significant difference between formulations for each of the most clinically important adverse events; with the exception of COPD exacerbations (4.1% for CFC-MDI group vs 2.4% in the HFA-MDI group; *P*=0.04). There was one death during the run in period of the trial (lung cancer), 5 deaths during the randomized phase: four of the 1,348 patients in HFA-MDI group (1 from a heart attack, 3 myocardial infarction), and one of 679 patients in the CFC-MDI group. There was no difference between the two groups in the incidence of serious adverse events and adverse events leading to withdrawal. Secondary: The use of rescue medication was similar in each treatment group. The analysis of FEV_1 and FVC showed that a fixed combination dose of fenoterol/ipratropium bromide delivered via HFA-MDI produced a comparable efficacy profile to delivery by CFC-MDI.

Drug regimen abbreviations: BID=twice daily, QID=four times daily, TID=three times daily,
Study abbreviations: CI=confidence interval, CR=case review, DB=double-blind, DD=double-dummy, IB=investigational blinded, MA=meta-analysis, MC=multicenter, OL=open-label, OR=odds ratio, OS=observational study, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, SB=single blinded, XO=crossover
Miscellaneous abbreviations: AUC=area under the curve, CBSQ=chronic bronchitis symptom questionnaire, CEAQ=clinic exercise-assessment questionnaire, CFC=chlorofluorocarbons, COPD=chronic obstructive pulmonary disease, CRDQ=chronic respiratory disease questionnaire, DPI=dry powered inhaler, ED=emergency department, FEV_1=forced expiratory volume in 1 second, FVC=forced vital capacity, HFA=hydrofluoroalkane, IC=inspiratory capacity, LABA=long acting β_2-agonists, LOS=length of stay, MDI=metered dose inhaler, PEF=peak expiratory flow, PEFR=peak expiratory flow rate, SABA=short acting β_2-agonists, SGRQ= St. George's Hospital Respiratory Questionnaire

Special Populations

Table 5. Special Populations[5-19]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Short Acting β_2-agonists					
Albuterol	Not sufficiently studied in patients ≥65 years old. Approved for use in children ≥4 years of age and older.	Use with caution in patients with renal dysfunction.	Not studied in patients with hepatic dysfunction.	C	Unknown; importance of drug administration to mother should be determined.
Levalbuterol	Not sufficiently studied in patients ≥65 years old. Safety and efficacy has not been established in children ≤4 years old.	Decrease in racemic albuterol clearance. Caution should be used when administering high doses of levalbuterol in patients with renal dysfunction.	Unknown; not studied in patients with hepatic dysfunction.	C	Yes (very low); importance of drug administration to mother should be determined.
Metaproterenol	Not sufficiently studied in patients ≥65 years old. Safety and efficacy has not been established in children ≤12 years old for the aerosol inhaler, and ≤6 years old for the nebulizer solution.	Not reported	Not reported	C	Unknown; importance of drug administration to mother should be determined.
Pirbuterol	Not sufficiently studied in patients ≥65 years old. Safety and efficacy has not been established in children ≤12 years old.	Not reported	Not reported	C	Unknown; importance of drug administration to mother should be determined.
Terbutaline	Not sufficiently studied in patients ≥65 years old. Safety and efficacy	Unknown; use with caution.	Unknown; use with caution.	B	Unknown; importance of drug administration to mother

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	has not been established in children ≤12 years old.				should be determined.
Long Acting β_2-agonists					
Arformoterol	When doses above 50 µg/day were administered, higher frequency of electrocardiogram ventricular ectopic changes occurred in the elderly. The safety and effectiveness has not been studied in the pediatric population.	Renal dose adjustment not required.	No dose adjustment required; use with caution in patients with hepatic dysfunction.	C	Unknown; importance of drug administration to mother should be determined.
Formoterol	No differences in safety and efficacy were observed between the elderly and younger patients. Safety and efficacy has not been established in children ≤5 years old.	Unknown; not studied in patients with renal dysfunction.	Unknown; not studied in patients with hepatic dysfunction.	C	Unknown; importance of drug administration to mother should be determined.
Salmeterol	Sufficiently studied in the elderly; no differences in safety was observed between the elderly and younger patients. Safety and efficacy has not been established in children ≤4 years old.	Unknown; not studied in patients with renal dysfunction	Unknown; hepatic dysfunction may lead to the accumulation of salmeterol. Use with caution in patients with hepatic dysfunction.	C	Yes (very low); importance of drug administration to mother should be determined.

Adverse Drug Events

Common adverse reactions reported with the single entity respiratory β_2-agonists are summarized in Table 6. The most common adverse events reported were related to the cardiovascular (i.e., palpitations, tachycardia) and central nervous systems (i.e., dizziness, headache, nervousness, tremor). The table below is indicative only of those with the highest reported frequency or those listed as most common.

Table 6. Adverse Drug Events (%) Reported with the Single Entity Respiratory β_2-Agonists[5-19]

Adverse Event(s)	Albuterol*	Albuterol†	Albuterol‡	Albuterol§	Arformoterol	Albuterol¶	Formoterol#	Levalbuterol‡	Levalbuterol¶	Metaproterenol *	Metaproterenol †	Metaproterenol ‡	Metaproterenol§	Pirbuterol§	Salmeterol#	Terbutaline†	Terbutaline**
Cardiovascular																	
Angina	✔	✔	-	✔	-	✔	✔	-	-	✔	-	-	-	-	-	-	-
Arrhythmias	✔	-	✔	✔	-	-	✔	-	-	✔	-	-	-	-	1-3	-	-
Chest pain	<1	✔	-	-	7	<3	1.9-3.2	<2	-	-	<1	-	-	<1	-	-	1.3-1.5
ECG abnormal	-	-	-	-	<2	-	-	<2	-	-	-	-	-	-	-	-	-
ECG change	-	-	-	-	<2	-	-	<2	-	-	-	-	-	-	-	-	-
Extrasystoles ventricular	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1.5	-
Hypertension	✔	✔	1	<5	-	✔	✔	<2	<2	✔	<1	<1	-	-	4	-	-
Hypotension	-	-	-	-	-	-	✔	<2	-	✔	-	-	-	<1	-	-	-
Pallor	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Palpitations	<1	2.4	-	<10	-	<3	✔	-	-	✔	3.8	<1	1-4	1.7	✔	5	7.8-22.9
Syncope	-	-	-	-	-	-	-	<2	-	-	-	-	-	-	-	-	-
Tachycardia	1-2	2.7	1	10	<2	7	✔	2.7-2.8	-	6.1	17.1	14	<1	1.2	✔	3.5	1.3-1.5
Vasodilations	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-
Central Nervous System																	
Anxiety	-	-	-	-	-	<3	1.5	<2.7	-	-	-	-	-	<1	1-3	1	✔
Asthenia	-	-	-	-	-	-	-	3	-	-	-	-	-	-	-	2	-
CNS stimulation	✔	✔	-	✔	-	✔	-	-	-	-	-	-	-	-	-	-	-
Confusion	-	-	-	-	-	-	-	-	-	-	-	-	-	<1	-	-	-
Depression	-	-	-	-	-	<3	-	-	-	-	-	-	-	<1	-	-	-
Dizziness	3	1.5	4	<5	-	<3	1.6	1.4-2.7	2.7	✔	2.4	-	1-4	1.2	4	3.5	1.3-10.2
Excitement	15	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Fatigue	1	-	-	-	-	-	✔	-	-	✔	1.4	-	-	-	-	-	11.7-9.8
Headache	4	18.8	3	✔	-	✔	✔	-	-	1.1	7	-	1-4	2	13-17	7.5	7.8-8.8
Hyperactivity	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hyperkinesia	4	-	-	-	-	<3	-	-	-	-	-	-	-	<1	-	-	-
Hypokinesia	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-	-

Adverse Event(s)	Albuterol*	Albuterol†	Albuterol‡	Albuterol§	Arformoterol	Albuterol¶	Formoterol#	Levalbuterol‡	Levalbuterol¶	Metaproterenol *	Metaproterenol †	Metaproterenol ‡	Metaproterenol§	Pirbuterol§	Salmeterol#	Terbutaline†	Terbutaline**
Insomnia	1	2.4	1	-	-	✔	1.5	<2	-	✔	1.8	-	-	<1	-	1.5	-
Irritable behavior	<1	✔	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Migraine	-	-	-	-	-	-	-	<2.7	-	-	-	-	-	-	-	-	-
Nervousness	9-15	8.5	-	<10	-	7	✔	2.8-9.6	✔	4.8	20.2	14	6.8	6.9	✔	35	16.9-30.7
Paresthesia	-	-	-	-	<2	-	-	<2	-	-	-	-	-	-	1-3	-	-
Sensory disturbances	-	-	-	-	-	-	-	-	-	-	<1	-	-	-	1-3	-	-
Shakiness	9	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Somnolence	-	0.3	-	-	<2	<3	-	-	-	-	<1	-	-	-	-	5.5	-
Sweating	<1	-	-	-	-	<3	-	-	-	-	-	-	-	-	-	1	<2.4
Tremor	10	24.2	20	<15	<2	-	1.9	<6.8	✔	1.6	16.9	5	1-4	6	✔	15	7.8-38
Vertigo	✔	✔	-	✔	-	✔	-	-	-	-	-	-	-	-	-	-	-
Weakness	<1	✔	-	-	-	-	-	-	-	-	<1	-	-	<1	-	-	0.5-1.3
Dermatological																	
Angioedema	✔	✔	-	✔	-	✔	-	-	-	-	-	-	-	-	✔	-	-
Contact dermatitis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1-3	-	-
Eczema	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1-3	-	-
Flushing	-	✔	-	-	-	-	-	-	-	-	-	-	-	<1	-	-	<2.4
Injection site pain	-	-	-	-	-	-	-	-	-	-	-		-	-	-	-	0.5-2.6
Photodermatitis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1-2	-	-
Pruritus	-	-	-	-	-	-	1.5	-	-	-	<1	-	-	<1	-	-	-
Rash	✔	✔	✔	✔	4	<3	1.1	<7.5	-	-	-	-	-	<1	1-3	-	-
Skin reaction	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	4	-	-
Urticaria	✔	✔	✔	✔	-	✔	-	<3	-	-	-	-	-	-	3	-	-
Endocrine and Metabolic																	
Decrease glucose intolerance	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-	-
Diabetes	-	-	-	-	-	<3	-	-	-	-	-	-	-	-	-	-	-
Hyperglycemia	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	1-3	-	-
Hypoglycemia	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-	-
Hyperlipidemia	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-	-
Gastrointestinal																	
Abdominal pain	-	-	-	-	-	-	-	<1.5	-	-	-	-	-	<1	-	-	-
Anorexia	-	-	-	-	-	-	-	-	-	-	-	-	-	<1	-	-	-
Constipation	-	-	-	-	<2	-	-	-	<2	-	-	-	-	-	-	-	-
Dental discomfort	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1-3	-	-
Diarrhea	-	-	-	6	-	-	-	1.5-6	-	-	1.2	-	-	<1	-	-	-

Adverse Event(s)	Albuterol*	Albuterol†	Albuterol‡	Albuterol§	Arformoterol	Albuterol¶	Formoterol#	Levalbuterol‡	Levalbuterol¶	Metaproterenol *	Metaproterenol †	Metaproterenol ‡	Metaproterenol§	Pirbuterol§	Salmeterol#	Terbutaline†	Terbutaline**
Dry mouth	✔	-	-	-	-	<3	1.2	<2	-	✔	<1	-	-	<1	-	1.5	✔
Dyspepsia	-	-	1	-	-	-	-	1.4-2.7	-	-	-	-	-	-	-	-	-
Dyspeptic symptoms	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1-3	-	-
Flatulence	-	-	-	-	-	<3	-	-	-	-	-	-	-	-	-	-	-
Gastroenteritis	-	-	-	-	-	-	-	<2	<2	-	-	-	-	-	-	-	-
Gastrointestinal infections	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1-3	-	-
Gastrointestinal symptoms/ distress	2	-	-	-	<2	-	-	-	-	-	3	-	1-4	-	1-3	-	-
Hyposalivation	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1-3	-	-
Increased appetite	3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Loss of appetite	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Nausea	-	4.2	4	<15	-	10	✔	<2	-	1.3	3.6	2	1-4	1.7	1-3	3	1.3-3.9
Oral candidiasis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1-3	-	-
Stomatitis	-	-	-	-	-	-	-	-	-	-	-	-	-	<1	-	-	-
Taste changes	-	✔	-	✔	-	4	-	-	-	-	-	<1	-	<1	-	-	-
Vomiting	✔	4.2	-	✔	-	7	-	-	10.5	-	<1	<1	1-4	<1	3		1.3-3.9
Genitourinary																	
Difficulty in micturition	-	✔	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Vaginal Moniliasis	-	-	-	-	-	-	-	-	<2	-	-	-	-	-	-	-	-
Urinary track infection	-	-	-	-	<2	3	-	-	-	-	-	-	-	-	-	-	-
Hematologic																	
Dysmenorrhea	-	-	-	-	-	-	-	-	<2	-	-	-	-	-	-	-	-
Hypersensitivity vasculitis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	<1	✔
Lymphadenopathy	-	-	-	-	-	-	-	<3	-	-	-	-	-	-	-	-	-
Laboratory Test Abnormalities																	
Hypokalemia	-	-	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	
Liver enzyme elevation	-	-	-	-	-	-	✔	-	-	-	-	-	-	-	-	<1	✔
Metabolic acidosis	-	-	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-
Musculoskeletal																	
Arthralgia	-	-	-	-	<2	-	-	-	-	-	-	-		-	1-2	-	-
Articular rheumatism	-	-	-	-	-	-	-	4.5-6.1	-	-	-	-	-	-	1-2	-	-
Leg cramps	-	-	-	-	4	<3	1.7	<2.7	-	-	-	-	-	-	-	-	-

Adverse Event(s)	Albuterol*	Albuterol†	Albuterol‡	Albuterol§	Arformoterol	Albuterol¶	Formoterol#	Levalbuterol‡	Levalbuterol¶	Metaproterenol *	Metaproterenol †	Metaproterenol ‡	Metaproterenol§	Pirbuterol§	Salmeterol#	Terbutaline†	Terbutaline**
Muscle cramps	-	2.7	-	-	-	-	1.7	-	-	-	-	-	-	-	3	-	✔
Muscle spasm	-	-	-	-	-	-	-	-	-	-	<1	-	-	-	3	-	-
Muscle stiffness	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1-3	-	-
Muscle tightness	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1-3	-	-
Muscle rigidity	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1-3	-	-
Musculoskeletal inflammation	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1-3	-	-
Myalgia	-	-	-	-	-	-	-	<1.5	<2	-	-	-	-	-	-	-	-
Pain	<1	-	-	-	8	-	-	1.5-3	4	-	<1	-	-	-	1-3	-	-
Respiratory																	
Asthma	-	-	-	-	-	-	-	9-9.1	9.4	-	2	-	1-4	-	3-4	-	-
Bronchitis	-	-	4	-	-	-	4.6	-	2.6	-	✔	-	-	-	7	-	-
Bronchospasm	✔	✔	8	✔	-	✔	-	-	-	-	✔	-	-	-	✔	-	-
Chest infection	-	-	-	-	-	-	2.7	-	-	-	-	-	-	-	-	-	-
Cough	<1	-	4	-	-	-	-	1.4-4.1	-	-	<1	-	1-4	1.2	>3	-	-
Drying of oropharynx	✔	✔	-	✔	-	✔	-	-	-	-	-	-	-	-	-	-	-
Dysphonia	-	-	-	-	-	<3	1	-	-	-	-	-	-	-	-	-	-
Dyspnea	-	-	-	-	4	-	2.1	-	-	-	✔	-	-	-	-	-	<2
Epistaxis	1	-	-	-	-	-	-	-	<2	-	-	-	-	-	-	-	-
Hoarseness	✔	-	✔	✔	<2	-	-	-	-	-	-	-	-	-	-	-	-
Increased sputum	-	-	-	-	-	-	1.5	-	-	-	-	-	-	-	-	-	-
Influenza	-	-	-	-	-	-	-	-	-	-	-	-	-	-	5	-	-
Laryngeal irritation	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1-3	-	-
Laryngeal spasm	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1-3	-	-
Laryngeal swelling	-	-	-	-	-	-	-	-		-	-	-	-	-	1-3	-	-
Nasal congestion	-	-	1	-	-	-	-	-	-	-	-	-	-	-	9	-	-
Oral mucosal abnormality-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1-3	-	-
Oropharyngeal edema	✔	✔	✔	-	-	✔	-	-	-	-	-	-	-	-	-	-	-
Pharyngitis	-	-	<1	-	-	-	3.5	3.0-10.4	6.6-7.9	-	-	-	-	-	6	-	-
Respiratory disorder	-	-	-	-	2	6	-	-	-	-	-	-	-	-	-	-	-
Rhinitis	-	-	-	-	-	16	-	2.7-11.1	7.4	-	-	-	-	-	5	-	-
Sinus headache	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1-3	-	-
Sinusitis	-	-	-	-	5	-	2.7	1.4-4.2	-	-	-	-	-	-	>3	-	-
Throat irritation	-	-	-	-	-	6	-	-	-	-	-	-	1-4	-	7	-	-
Viral respiratory infection	-	-	-	-	-	21	7.4	6.9-12.3	-	-	-	-	-	-	>3	-	-
Wheezing	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Adverse Event(s)	Albuterol*	Albuterol†	Albuterol‡	Albuterol§	Arformoterol	Albuterol¶	Formoterol#	Levalbuterol‡	Levalbuterol¶	Metaproterenol *	Metaproterenol †	Metaproterenol ‡	Metaproterenol§	Pirbuterol§	Salmeterol#	Terbutaline†	Terbutaline**
Other																	
Accidental injury	-	-	-	-	-	-	-	<2.7	9.2	-	-	-	-	-	-	-	-
Acne	-	-	-	-	-	-	-	-	<2	-	-	-	-	-	-	-	-
Allergic reaction	-	-	-		-	6	-	-	-	-	-	-	-	-	-	-	-
Anaphylaxis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1-3	-	-
Back pain	-	-	-	-	6	4	4.2	-	-	-	-	-	-	-	-	-	-
Conjunctivitis	1	-	-	-	-	-	-	-	<2	-	-	-	-	-	-	-	-
Cyst	-	-	-	-	-	-	-	-	<2	-	-	-	-	-	-	-	-
Ear pain	-	-	-	-	-	-	-	-	<2	-	-	-	-	-	-	-	-
Ear signs	-	-	-	-	-	-	-	-	-	-	-	-	-	-	4	-	-
Edema	-	-	-	✔	3	<3	-	1.4-2.8	-	-	-	-	-	-	1-3	-	-
Eye itch	-	-	-	-	-	-	-	<2	-	-	-	-	-	-	-	-	-
Fever	-	-	-	-	<2	6	2.2	3-9.1	-	-	-	-	-	-	1-3	-	-
Flu syndrome	-	-	-	-	3	-	-	1.4-4.2	<2	-	-	-	-	-	-	-	-
Tonsillitis	-	-	-	-	-	-	1.2	-	-	-	-	-	-	-	-	-	-
Trauma	-	-	-	-	-	-	1.2	-	-	-	-	-	-	-	-	-	-
Viral infection	-	-	-	-	-	-	17.2	7.6-9	<2	-	-	-	-	-	-	-	-

CNS=central nervous system, ECG=electrocardiogram
✔ Percent not specified.
- Event not reported.
* Oral syrup formulation.
† Oral tablet formulation.
‡ Inhalation solution formulation.
§ Aerosol inhalation formulation.
¶ HFA aerosol inhalation formulation.
# Dry powder inhaler.
** Injection.

Contraindications / Precautions[5-19]

β_2-agonist: In some patients, the use of β_2-agonists have been reported to produce electrocardiogram changes such as flattening of the T-wave, prolongation of the QTc interval, and ST segment depression. β_2-agonists can produce clinically significant cardiovascular effects in some patients (i.e., increase pulse rate and blood pressure). In some patients, the use of β_2-agonists can produce paradoxical bronchospasm, which may be life threatening. Immediate discontinuation of the medication should occur if paradoxical bronchospasm is suspected.

Black Box Warning for Long-acting β_2-agonists

Long-Acting β_2-agonists may increase the risk of asthma related deaths
Long-acting β_2-agonists may increase the risk of asthma-related death. Therefore, when treating patients with asthma, only use arformoterol, formoterol, and salmeterol as additional therapy for patients not adequately controlled on other asthma-controller medications (i.e., low- to med-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies, included β_2-agonists. Data from a large placebo-controlled U.S. study that compared the safety and of salmeterol or placebo added to the usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol.

Drug Interactions

Significant drug interactions with the single entity respiratory β_2-agonists are summarized in Table 7.

Table 7. Drug Interactions[5-19]

Generic Name	Interacting Medication or Disease	Potential Result
β_2-agonists (all)	Diuretics (i.e., loop diuretics, thiazide diuretics)	Electrocardiogram changes or hypokalemia may potentially be worsened with the addition of a β_2-agonist, particularly when the recommended dose is exceeded.
β_2-agonists (all)	Monoamine oxidase inhibitors	Monoamine oxidase is an enzyme that metabolizes catecholamines. When given with an indirect acting sympathomimetic, hypertensive crisis may occur.
β_2-agonists (all)	Nonselective β_2-agonists blocking agents	β-blockers inhibit the therapeutic effects of β_2 agonists and may produce bronchospasm in patients with asthma and chronic obstructive pulmonary disease.
β_2-agonists (all)	Tricyclic antidepressants	Tricyclic antidepressant may potentiate the cardiovascular effects of β_2-agonists.

Dosage and Administration

Table 8. Dosing and Administration[5-19]

Generic Name	Adult Dose	Pediatric Dose	Availability
Short Acting β_2-agonists			
Albuterol	Asthma, nocturnal asthma, and reversible bronchospasm: Syrup: 2-4 mg (5-10 mL) 3-4 times daily; maximum, 8 mg (20 mL) 4 times daily Sustained-release tablet: 4-8 mg every 12 hours; maximum, 32 mg daily in divided doses	Asthma, nocturnal asthma, and reversible bronchospasm: Syrup: 2-5 years of age: 0.1 mg/kg of body weight 3 times daily; maximum, 4 mg 3 times daily; 6-14 years of age: 2 mg 3-4 times daily; maximum, 24 mg daily in divided doses	Syrup: 2 mg/5 mL Sustained-release tablet: 4 mg 8 mg Nebulization solution (3 mL unit dose vials): 1.25 mg 0.63 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	Inhalation solution: 2.5 mg 3-4 times daily Aerosol inhaler (HFA): 1-2 inhalations (120-240 µg) every 4-6 hours; maximum, 12 inhalations daily Exercise-induced bronchospasm: Aerosol inhaler (HFA): 2 inhalations (240 µg) 15-30 minutes before exercise	Sustained-release tablet: 6-12 years of age: 4 mg every 12 hours; maximum, 24 mg daily in divided doses Inhalation solution: 2-12 years of age: 0.63-1.25 mg 3-4 times daily; maximum, 2.5 mg 3-4 times daily Aerosol inhaler: Safety and efficacy in children less than 12 years of age have not been established. Aerosol inhaler (HFA): Children 4 years of age and older are approved to use adult dose.	0.5% concentrated solution MDI (200 inhalations): 120 µg albuterol sulfate*
Levalbuterol	Asthma, nocturnal asthma, and reversible bronchospasm: Inhalation solution: 0.63 mg 3 times daily every 6-8 hours; maximum, 1.25 mg 3 times daily Aerosol inhaler (HFA): 1-2 inhalations (59-118 µg) every 4-6 hours; maximum, 12 inhalations daily	Asthma, nocturnal asthma, and reversible bronchospasm: Inhalation solution: 6-11 years of age: 0.31 mg 3 times daily; maximum, 0.63 mg 3 times daily Aerosol inhaler (HFA): Children 4 years of age and older are approved to use adult dose.	Nebulization solution (3 mL vials): 0.31 mg 0.63 mg 1.25 mg MDI (200 inhalations): 59 µg†
Metaproterenol	Asthma, nocturnal asthma, and reversible bronchospasm: Syrup: 20 mg (10 mL) 3-4 times daily; maximum, titrated to patient's response Tablet: 20 mg 3-4 times daily; maximum, titrated to patient's response Inhalation solution: 10-15 mg administered 3-4 times daily; maximum, titrated to patient's response Aerosol inhaler: 2-3 inhalations (1.3-1.95 mg) repeated every 3-4 hours; maximum, 12 inhalations daily	Asthma, nocturnal asthma, and reversible bronchospasm: Syrup: 6-9 years of age (or weight under 60 lb): 10 mg 3-4 times daily; children 9 years of age (or weight over 60 lb) and older approved for use adult dose Tablet: 6-9 years of age (or weight under 60 lb): 1 teaspoonful 3-4 times daily Children 9 years of age (or weight over 60 lb) and older are approved to use adult dose.	Syrup: 10 mg/5 mL Tablet: 10 mg 20 mg Nebulization solution: 0.4% (10 mg) 0.6% (15 mg) MDI (200 inhalations): 0.65 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
		Inhalation solution: Safety and efficacy in children less than 12 years of age have not been established. Aerosol inhaler: Safety and efficacy in children less than 12 years of age have not been established.	
Pirbuterol	Asthma, nocturnal asthma, and reversible bronchospasm: 1-2 inhalations (200-400 µg) repeated every 4-6 hours; maximum, 12 inhalations daily	Safety and efficacy in children less than 12 years of age have not been established.	Breath activated aerosol inhaler (80 inhalations and 400 inhalations): 200 µg
Terbutaline	Asthma, nocturnal asthma, and reversible bronchospasm: Injection: 0.25 mg injected into the deltoid, may repeat in 15-30 minutes if no clinical improvement; maximum, 0.5 mg every 4 hours Tablet: 2.5-5 mg repeated every 6 hours 3 times daily; maximum, 15 mg daily	Asthma, nocturnal asthma, and reversible bronchospasm: Injection: Safety and efficacy in children less than 12 years of age have not been established. Tablet: Safety and efficacy in children less than 12 years of age have not been established; Children 12-15 years of age: 2.5 mg repeated every 6 hours 3 times daily; maximum, 2.5 mg daily	Injection (2 mL vial): 1 mg/mL Tablet: 2.5 mg 5 mg
Long Acting β_2-agonists			
Arformoterol	Chronic obstructive pulmonary disease: Inhalation solution: 15 µg/2 mL twice daily	Safety and efficacy in children has not been established.	Nebulization solution (2 mL vials): 15 µg
Formoterol	Asthma, nocturnal asthma, and reversible bronchospasm: One 12 µg capsule inhaled every 12 hours; maximum, 2 inhalations daily (24 µg) Exercise-induced bronchospasm: One 12 µg capsule inhaled at least 15 minutes before exercise (no repeat dose)	Children 5 years of age and older are approved to use adult dose.	Capsule for inhalation: 12 µg
Salmeterol	Asthma, nocturnal asthma, and reversible bronchospasm: 1 inhalation (50 µg) 2 times	Children 4 years of age and older are approved to use adult dose.	DPI (28 and 60 inhalations): 50 µg

Generic Name	Adult Dose	Pediatric Dose	Availability
	daily Exercise-induced bronchospasm: 1 inhalation (50 µg) at least 30 minutes before exercise (no repeat dose)		

DPI=dry powder inhalation, HFA=hydrofluoroalkanes, MDI=metered dose inhaler.
*Delivering 108 µg of albuterol (90 µg albuterol base).
†Delivering 45 µg levalbuterol base.

Clinical Guidelines

Table 9. Clinical Guidelines

Clinical Guidelines	Recommendations
The National Heart, Lung, and Blood Institute (NHLBI)/ National Asthma Education and Prevention Program (NAEPP): **Guidelines for the Diagnosis and Management of Asthma (2007)**[1]	Diagnosis • To establish a diagnosis of asthma, a clinician must determine the presence of episodic symptoms or airflow obstruction, partially reversible airflow obstruction, and alternate diagnoses must be excluded. • The recommended methods to establish a diagnosis are a detailed medical history, physical exam focusing on the upper respiratory tract, spirometry to demonstrate obstruction and assess reversibility, and additional studies to exclude alternate diagnoses. • A diagnosis of asthma should be considered if any of the following indicators are present: wheezing, history of cough, recurrent wheeze, difficulty breathing or chest tightness, symptoms that occur or worsen with exercise or viral infections, and symptoms that occur or worsen at night. • Spirometry is needed to establish a diagnosis of asthma. • Additional studies such as additional pulmonary function tests, bronchoprovocation, chest x-ray, allergy testing, and biomarkers of inflammation may be useful when considering alternative diagnoses. Treatment • Pharmacologic therapy is used to prevent and control asthma symptoms, improve quality of life, reduce the frequency and severity of asthma exacerbations, and reverse airflow obstruction. • For initiating treatment, asthma severity should be classified, and the initial treatment should correspond to the appropriate severity category. • Long-term control medications such as inhaled corticosteroids (ICSs), long-acting bronchodilators, leukotriene modifiers, cromolyn, theophylline, and immunomodulators should be taken daily on a long-term basis to achieve and maintain control of persistent asthma. • Quick-relief medications are used to provide prompt relief of bronchoconstriction and accompanying acute symptoms such as cough, chest tightness, and wheezing. • Quick relief medications include short-acting β_2-agonists (SABAs), anticholinergics, and systemic corticosteroids. Long-term Control Medications • ICSs are the most potent and consistently effective long-term control medication for asthma in patients of all ages. • Short courses of oral systemic corticosteroids may be used to gain prompt control when initiating long-term therapy and chronic administration is only

Clinical Guidelines	Recommendations
	used for the most severe, difficult-to-control asthma. • When patients ≥12 years of age require more than low-dose ICSs, the addition of a long-acting β_2-agonist (LABA) is recommended. Alternative, but not preferred, adjunctive therapies include leukotriene receptor antagonists (LTRAs), theophylline, or in adults, zileuton. • Mast cell stabilizers (cromolyn and nedocromil) are used as alternatives for the treatment of mild persistent asthma. They can also be used as preventative treatment prior to exercise or unavoidable exposure to known allergens. • Omalizumab, an immunomodulator, is used as adjunctive therapy in patients ≥12 years old who have allergies and severe persistent asthma that is not adequately controlled with the combination of high-dose ICS and LABA therapy. • LTRAs (montelukast and zafirlukast) are alternative therapies for the treatment of mild persistent asthma. • LABAs (salmeterol and formoterol) are not to be used as monotherapy for long-term control of persistent asthma. • LABAs should continue to be considered for adjunctive therapy in patients ≥5 years of age who have asthma that require more than low-dose ICSs. For patients inadequately controlled on low-dose ICSs, the option to increase the ICS should be given equal weight to the addition of a LABA. • Methylxanthines, such as sustained-release theophylline, may be used as an alternative treatment for mild persistent asthma. • Tiotropium bromide is a long-acting inhaled anticholinergic indicated once-daily for chronic obstructive pulmonary disease and has not been studied in the long-term management of asthma. <u>Quick-relief Medications</u> • SABAs are the therapy of choice for relief of acute symptoms and prevention of exercise induced bronchospasm. • There is inconsistent data regarding the superior efficacy of levalbuterol over albuterol. Some studies suggest an improved efficacy while other studies fail to detect any advantage of levalbuterol. • Anticholinergics may be used as an alternative bronchodilator for patients who do not tolerate SABAs and provide additive benefit to SABAs in moderate-to-severe asthma exacerbations. • Systemic corticosteroids are used for moderate and severe exacerbations as adjunct to SABAs to speed recovery and prevent recurrence of exacerbations. • The use of LABAs is not currently recommended to treat acute symptoms or exacerbations of asthma. <u>Assessment, Treatment, and Monitoring</u> • A stepwise approach to managing asthma is recommended to gain and maintain control of asthma in both the impairment and risk domains. • Regularly scheduled, daily, chronic use of a SABA is not recommended. Increased use or SABA use >2 days a week for symptom relief generally indicates inadequate asthma control.

<table>
<tr><th>Clinical Guidelines</th><th>Recommendations</th></tr>
<tr><td></td><td>
• The stepwise approach for managing asthma is outlined below:
<table>
<tr><th>Inter-mittent Asthma</th><th colspan="5">Persistent Asthma: Daily Medication</th></tr>
<tr><th>Step 1</th><th>Step 2</th><th>Step 3</th><th>Step 4</th><th>Step 5</th><th>Step 6</th></tr>
<tr><td><u>Preferred</u>
SABA as needed</td><td><u>Preferred</u>
Low-dose ICS

<u>Alternative</u>
Cromolyn, LTRA, nedocromil, or theophylline</td><td><u>Preferred</u>
Low-dose ICS+LABA OR medium-dose ICS

<u>Alternative</u>
Low-dose ICS+either a LTRA, theophylline, or zileuton</td><td><u>Preferred</u>
Medium-dose ICS+LABA

<u>Alternative</u>
Medium-dose ICS+either a LTRA, theophylline, or zileuton</td><td><u>Preferred</u>
High-dose ICS+LABA AND consider omalizumab for patients who have allergies</td><td><u>Preferred</u>
High-dose ICS+LABA+ oral steroid AND consider omalizumab for patients who have allergies</td></tr>
</table>
<u>Management of Exacerbations</u>
• Appropriate intensification of therapy by increasing inhaled SABAs and, in some cases, adding a short course of oral systemic corticosteroids is recommended.

<u>Special Populations</u>
• For exercise induced bronchospasm, pretreatment before exercise with either a SABA or LABA is recommended. LTRAs may also attenuate exercise induced bronchospasm and mast cell stabilizers can be taken shortly before exercise as an alternative treatment for prevention however, they are not as effective as SABAs. The addition of cromolyn to a SABA is helpful in some individuals who have exercise induced bronchospasm.
• Consideration of the risk for specific complications must be given to patients who have asthma who are undergoing surgery.
• Albuterol is the preferred SABA in pregnancy because of an excellent safety profile.
• ICSs are the preferred treatment for long-term control medication in pregnancy. Specifically, budesonide is the preferred ICS as more data is available on using budesonide in pregnant women than other ICSs.
</td></tr>
<tr><td>Global Initiative for Asthma (GINA): Global Strategy for Asthma Management and Prevention (2008)[2]</td><td>
<u>Diagnosis</u>
• A clinical diagnosis of asthma is often prompted by symptoms such as episodic breathlessness, wheezing, cough, and chest tightness.
• Measurements of lung function (spirometry or peak expiratory flow) provide an assessment of the severity of airflow limitation, its reversibility, and its variability and provide confirmation of the diagnosis of asthma.

<u>Treatment</u>
• Education should be an integral part of all interactions between health care professionals and patients, and is relevant to asthma patients of all ages.
• Measures to prevent the development of asthma, asthma symptoms, and asthma exacerbations by avoiding or reducing exposure to risk factors should be implemented whenever possible.
• Controller medications are administered daily on a long-term basis and include inhaled and systemic glucocorticosteroids, leukotriene modifiers, LABAs in combination with inhaled glucocorticosteroids, sustained-released theophylline, cromones, and anti-immunoglobulin E (IgE).
• Reliever medications are administered on an as-needed basis to reverse bronchoconstriction and relieve symptoms and include rapid-acting inhaled
</td></tr>
</table>

Clinical Guidelines	Recommendations
	β_2-agonists, inhaled anticholinergics, short-acting theophylline, and SABAs. Controller Medications • Inhaled glucocorticosteroids are currently the most effective anti-inflammatory medications for the treatment of persistent asthma for patients of all ages. • Inhaled glucocorticosteroids differ in potency and bioavailability, but few studies have confirmed the clinical relevance of these differences. • To reach clinical control, add-on therapy with another class of controller is preferred over increasing the dose of inhaled glucocorticosteroids. • Leukotriene modifiers are generally less effective than inhaled glucocorticosteroids therefore may be used as an alternative treatment in patients with mild persistent asthma. • Some patients with aspirin-sensitive asthma respond well to leukotriene modifiers. • Leukotriene modifiers used as add-on therapy may reduce the dose of inhaled glucocorticosteroids required by patients with moderate to severe asthma, and may improve asthma control in adult patients whose asthma is not controlled with low or high doses of inhaled glucocorticosteroids. • Several studies have demonstrated that leukotriene modifiers are less effective than LABAs as add-on therapy. • LABAs should not be used as monotherapy in patients with asthma as these medications do not appear to influence asthma airway inflammation. • When a medium dose of an inhaled glucocorticosteroid fails to achieve control, the addition of a LABA is the preferred treatment. • Controlled studies have shown that delivering a LABA and an inhaled glucocorticosteroid in a combination inhaler is as effective as giving each drug separately. Fixed combination inhalers are more convenient, may increase compliance, and ensure that the LABA is always accompanied by a glucocorticosteroid. • Although the guideline indicates that combination inhalers containing formoterol and budesonide may be used for both rescue and maintenance, this use is not approved by the Food and Drug Administration (FDA). • Theophylline as add-on therapy is less effective than LABAs but may provide benefit in patients who do not achieve control on inhaled glucocorticosteroids alone. • Cromolyn and nedocromil are less effective than a low dose of an inhaled glucocorticosteroid. • Oral LABA therapy is used only on rare occasions when additional bronchodilation is needed. • Anti-IgE treatment with omalizumab is limited to patients with elevated serum levels of IgE. • Long-term oral glucocorticosteroid therapy may be required for severely uncontrolled asthma, but is limited by the risk of significant adverse effects. • Other anti-allergic compounds have limited effect in the management of asthma. Reliever Medications • Rapid-acting inhaled β_2-agonists are the medications of choice for the relief of bronchospasm during acute exacerbations and for the pretreatment of exercise-induced bronchoconstriction, in patients of all ages. • Rapid-acting inhaled β_2-agonists should be used only on an as-needed

<table>
<tr><th>Clinical Guidelines</th><th>Recommendations</th></tr>
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basis at the lowest dose and frequency required.
• Although the guidelines states that formoterol, a LABA, is approved for symptom relief because of its rapid onset of action, and that it should only be used for this purpose in patients on regular controller therapy with inhaled glucocorticosteroids, the use of this agent as a rescue inhaler is not approved by the FDA.
• Ipratropium bromide, an inhaled anticholinergic, is a less effective reliever medication in asthma than rapid-acting inhaled β_2-agonists.
• Short-acting theophylline may be considered for relief of asthma symptoms.
• Short-acting oral β_2-agonists (tablets, solution, etc.) are appropriate for use in patients who are unable to use inhaled medication however, they are associated with a higher prevalence of adverse effects.
• Systemic glucocorticosteroids are important in the treatment of severe acute exacerbations.

<u>Assessment, Treatment, and Monitoring</u>
• The goal of asthma treatment is to achieve and maintain clinical control.
• To aid in clinical management, a classification of asthma by level of control is recommended: controlled, partly controlled, or uncontrolled.
• Treatment should be adjusted in a continuous cycle driven by the patient's asthma control status and treatment should be stepped up until control is achieved. When control is maintained for at least three months, treatment can be stepped down.
• Increased use, especially daily use, of reliever medication is a warning of deterioration of asthma control and indicates the need to reassess treatment.
• The management approach based on control is outlined below:
<table>
<tr><th>Step 1</th><th>Step 2</th><th>Step 3</th><th>Step 4</th><th>Step 5</th></tr>
<tr><td colspan="5">Asthma education and environmental control</td></tr>
<tr><td colspan="5">As needed rapid-acting β_2-agonist</td></tr>
<tr><td rowspan="5">Controller options</td><td>Select one</td><td colspan="2">Select one</td><td>Add one or more</td><td>Add one or both</td></tr>
<tr><td>Low-dose inhaled glucocortico-steroid</td><td colspan="2">Low-dose inhaled glucocorticosteroid +LABA</td><td>Medium- or high-dose inhaled glucocortico-steroid+LABA</td><td>Oral glucocorticosteroid</td></tr>
<tr><td>Leukotriene modifier</td><td colspan="2">Medium- or high-dose inhaled glucocorticosteroid</td><td>Leukotriene modifier</td><td>Anti-IgE treatment</td></tr>
<tr><td>-</td><td colspan="2">Low-dose inhaled glucocorticosteroids +leukotriene modifier</td><td>-</td><td>-</td></tr>
<tr><td>-</td><td colspan="2">Low-dose inhaled glucocorticosteroid +sustained-release theophylline</td><td>-</td><td>-</td></tr>
</table>

<u>Management of exacerbations</u>
• Repeated administration of rapid-acting inhaled β_2-agonists is the best method of achieving relief for mile to moderate exacerbations.
• Systemic glucocorticosteroids should be considered if the patient does not immediately respond to rapid-acting inhaled β_2-agonists or if the episode is severe.
</td></tr>
</table>

Clinical Guidelines	Recommendations
	Special Populations • LABAs may also be used to prevent exercise induced bronchospasm and because of a more rapid onset of action, formoterol is more suitable for symptom relief as well as symptom prevention over salmeterol. • Appropriately monitored use of theophylline, inhaled glucocorticosteroids, β_2-agonists, and leukotriene modifiers, specifically montelukast, are not associated with an increased incidence of fetal abnormalities. • Inhaled glucocorticosteroids have been shown to prevent exacerbations of asthma during pregnancy. • Acute exacerbations during pregnancy should be treated with nebulized rapid-acting β_2-agonists and oxygen. Systemic glucocorticosteroids should be instituted when necessary.
Global Initiative for Chronic Obstructive Lung Disease (GOLD): **Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (COPD) (2008)**[19]	Diagnosis • A clinical diagnosis of COPD should be considered in any patient who has chronic cough, dyspnea, excess sputum production, or history of exposure to risk factors including smoking. • A diagnosis of COPD should be confirmed by spirometry. • COPD patients typically display a decrease in both Forced Expiratory Volume in one second (FEV_1) and FEV_1/ Forced Vital Capacity (FVC) ratio. • The presence of a post-bronchodilator $FEV_1/FVC<0.70$ and $FEV_1<80\%$ predicted confirms the presence of airflow limitation that is not fully reversible. • A detailed medical history should be obtained for all patients suspected of developing COPD. • Severity of COPD is based on the level of symptoms, the severity of the spirometric abnormality, and the presence of complications. • Bronchodilator reversibility testing should be performed to rule out the possibility of asthma. • Chest radiograph may be useful to rule out other diagnoses. • Arterial blood gas measurements should be performed in advanced COPD. • Screening for α_1-antitrypsin deficiency should be performed in patients of Caucasian decent who develop COPD at 45 years of age or younger. • Differential diagnoses should rule out asthma, congestive heart failure, bronchiectasis, tuberculosis, diffuse panbronchiolitis, and obliterative bronchiolitis. Treatment • Patients should be instructed to avoid the exacerbating exposure. This includes assisting the patient in smoking cessation attempts and counseling the patient on how to avoid pollutant exposures. • The management of COPD should be individualized to address symptoms and improve the patient's quality of life. • None of the medications for COPD have been shown to modify long-term decline in lung function. Treatment should be focused on reducing symptoms and complications. • Administer bronchodilator medications on an as needed or regular basis to prevent or reduce symptoms and exacerbations. • Principle bronchodilators include β_2-agonists, anticholinergics and theophylline used as monotherapy or in combination. • The use of long-acting bronchodilators is more effective and convenient than short-acting bronchodilators. • For single-dose, as needed use, there is no advantage in using levalbuterol

Clinical Guidelines	Recommendations
	over conventional nebulized bronchodilators. • Inhaled corticosteroids should be used in patients with an FEV_1<50% of the predicted value. • Chronic treatment with systemic corticosteroids should be avoided due to an unfavorable risk-benefit ratio. • COPD patients should receive an annual influenza vaccine. • The pneumococcal polysaccharide vaccine is recommended for COPD patients ≥65 years old or for patients <65 years old with an FEV_1<40% of the predicted value. • Exercise training programs should be implemented for all COPD patients. • Long-term administration of oxygen (>15 hours/day) increases survival in patients with chronic respiratory failure. Management of Exacerbations • The most common causes of an exacerbation are bronchial tree infections and air pollution. • Inhaled β_2-agonists, with or without anticholinergics, and systemic corticosteroids are effective treatments for exacerbations of COPD. • Patients experiencing COPD exacerbations with clinical signs of airway infection may benefit from antibiotic treatment.
National Institute for Clinical Excellence (NICE): **COPD: National Guideline on the Management of COPD in Adults in Primary and Secondary Care (2004)**[20]	Diagnosis • Diagnosis should be considered in patients >35 years of age who have a risk factor for the development of COPD. • The primary risk factor is smoking. • Spirometry is diagnostic of airflow obstruction. Airflow obstruction is defined as FEV_1<80% predicted and FEV_1/FVC<70%. Treatment • Smoking cessation should be encouraged for all patients with COPD. • Short-acting bronchodilators, as necessary, should be the initial empiric treatment for t he relief of breathlessness and exercise limitation. • Long-acting bronchodilators (beta$_2$ agonists and/or anticholinergics) should be given to patients who remain symptomatic even with short-acting bronchodilators, if two or more exacerbations occur per year. • Inhaled corticosteroids should be added to patients on long-acting bronchodilators to decrease the frequency of exacerbations in patients with an $FEV_1 \leq 50\%$ of the predicted value. • Oral corticosteroids should be reserved for those patients with advanced COPD. • Theophylline should only be used after a trial of long-acting and short-acting bronchodilators or if the patient is unable to take inhaled therapy. Plasma levels must be measured since there is a larger side effect burden with theophylline. • Pulmonary rehabilitation should be made available to patients. • Noninvasive ventilation should be used for patients with persistent hypercapnic respiratory failure. Management of Exacerbations • Patients with exacerbations should be evaluated for hospital admission. • Patients should receive a chest radiograph, have arterial blood gases monitored, have sputum cultured if it is purulent, and have blood cultures taken if pyrexial.

Clinical Guidelines	Recommendations
	• Oral corticosteroids should be used in all patients admitted to the hospital who do not have contraindications to therapy. The course of therapy should be no longer than 14 days. • Oxygen should be given to maintain oxygen saturation above 90%. • Patients should receive invasive and noninvasive ventilation as necessary. • Respiratory physiotherapy may be used to help remove sputum. • Before discharge, patients should be evaluated by spirometry. • Patients should be properly educated on their inhaler technique and the necessity of usage and should schedule a follow up appointment with a health care professional.

Conclusions

The single entity respiratory β_2-agonists are Food and Drug Administration (FDA) approved for the treatment of asthma, chronic obstructive pulmonary disorder (COPD), reversible airway obstruction and/or exercise-induced asthma (EIA).[5-19] These agents can be separated into short-acting and long-acting respiratory β_2-agonists due to their pharmacokinetic differences. These agents are available in a variety of dosage forms including solution for nebulization, aerosol inhaler, dry powder inhaler, oral solution, tablet, and solution for injection. Short-acting respiratory β_2-agonists are available generically; however, there are no generic formulations for the long-acting respiratory β_2-agonists.

The National Heart, Lung, and Blood Institute (NHLBI)/National Asthma Education and Prevention Program (NAEPP) guidelines, as well as other national and international guidelines, recommend the use of short-acting β_2-agonists for patients in all stages of asthma, for symptomatic relief of reversible airway disease, and for exercise-induced bronchospasm.[1,2,68-71] These medications should be used on an as-needed or "rescue" basis. In the chronic management of asthma the long-acting agents should be used as add-on therapy in patients not adequately controlled on an inhaled corticosteroid as an alternative to maximizing the dose of the inhaled corticosteroid.[1,2] Overall, short-acting β_2-agonists demonstrated similar efficacy and safety.[21-32,36] Long-acting agents have been shown to be more efficacious than routine regimens with short-acting agents.[33-53] However, in the treatment of asthma, long-acting β_2-agonists should not be used as monotherapy or as rescue medications due to the potential risk of asthma-related deaths.[33,41]

Long-acting β_2-agonists can also be used for exercise-induced bronchospasm and provide a longer period of coverage (typically 12 hours). Guidelines do not recommend one long acting agent over another, and head-to-head clinical trials have been inconclusive to determine preferential status of any one agent. [52-66]

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) and National Institute for Clinical Excellence (NICE) guidelines state that these long-acting agents also have a role in the treatment of COPD for patients who remain symptomatic even with current treatment with short-acting bronchodilators.[3,4] These agents can be added to other regimens, including an anticholinergic agent, in efforts to decrease exacerbations.[3,4] Guidelines and the results from clinical trials do not determine preferential status of any one long-acting agent.[3,4,56-61]

The respiratory β_2-agonists share similar drug-to-drug interactions and have similar adverse events.[5-19] Some of the most common adverse events include palpitations, dizziness, nervousness, headache, tachycardia, and nausea.[5-19]

In conclusion, all short-acting respiratory β_2-agonists brand products within the class reviewed are comparable to each other and to the generics in this class and offer no significant clinical advantage over other alternatives in general use. The long-acting β_2-agonist brand products within the class reviewed offer clinical advantages over the short-acting β_2-agonists for the treatment of COPD and EIA, and are

considered comparable to each other. However, the long-acting respiratory β_2-agonists are considered add-on therapy and are not considered first-line agents for general use.

Recommendations

Based on the information presented in the review above and cost considerations, no changes are recommended to the current approval criteria.

Non-preferred short-acting beta-adrenergic metered dose inhalers (Alupent®, Proair® HFA, Proventil® HFA, Ventolin® HFA) require prior authorization with the following approval criteria:

- A patient must be started and stabilized on the requested medication.

OR

- A patient must have a documented side effect, allergy, or treatment failure to Xopenex®.

All long-acting beta-adrenergic metered dose inhalers (Serevent® Diskus, Foradil®) are preferred on the OVHA PDL after the following prior authorization approval criteria are met:

- A patient has a diagnosis of COPD

OR

- A patient has a diagnosis of asthma and prescribed a controller medication.

Accuneb® nebulizer solution 0.63 mg/ml and 1.25 mg/ml requires prior authorization with the following approval criteria:

- The patient must have a documented intolerance to the generic formulation.

Xopenex® nebulizer solution 0.63 mg/ml and 1.25 mg/ml, for patients over the age of 12, requires prior authorization with the following approval criteria:

- The patient must have been started and stabilized on the requested medication.

OR

- The patient must have had a documented side effect, allergy, or treatment failure to Accuneb®, generic albuterol nebulizer solution 0.83 mg/ml. or metaproterenol neb solution.

Brovana® or Perforomist® nebulizer solution requires prior authorization with the following approval criteria:

- The patient must have a diagnosis of COPD**.**

AND

- The patient must be unable to use a non-nebulized long-acting bronchodilator or anticholinergic (Foradil®, Serevent® or Spiriva®) due to a physical limitation

Brethine® tablets require prior authorization with the following approval criteria:

- The patient must have had a documented side effect, allergy, or treatment failure to generic terbutaline tablets.

Vospire ER® tablets require prior authorization with the following approval criteria:

- The patient must have had a documented side effect, allergy, or treatment failure to generic albuterol ER tablets.

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